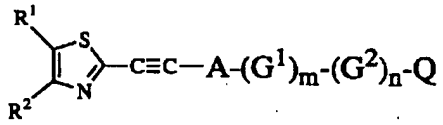
(57) (Abstract)

Object

To put forward a compound useful as effective ingredient of the prevention and/or therapy drug of allergic disease co-having leukotriene antagonism and histamine release inhibitory action from mast cell.

Method of Solution

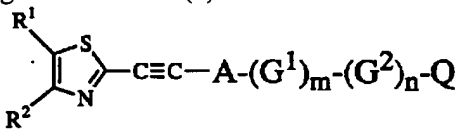
A compound and the salts thereof represented by formula (1) [R1 and R2 denote hydrogen atom, halogen atom, alkyl group optionally having substituent or the like, A denotes a phenyl group, pyridyl group optionally having substituent or the like, G1 denotes an oxygen atom, carbonyl group, ethynyl group or the like, G2 denotes a phenyl group, pyridyl group optionally having substituent or the like, m and n denote 0 or 1, and Q denotes alkoxycarbonyl group optionally having substituent, carboxyl group or the like].



(1)

Claim 1

A compound represented by general formula (1) and salts thereof



(1)

(wherein, R1 and R2 each independently denote hydrogen atom, halogen atom, optionally substituted alkyl group, optionally substituted cycloalkyl group, or a ring formed by linking R1 and R2 together. A denotes optionally substituted phenyl group, optionally substituted pyridyl group, optionally substituted furyl group, optionally substituted thienyl group, optionally substituted benzofuranyl group, optionally substituted benzo (b) thienyl group, optionally substituted benzoxazolyl group, optionally substituted benzothiazolyl group, optionally substituted pyrido (1,2-a) pyrimidinyl group, optionally substituted quinazolinyl group, optionally substituted benzo triazinyl group or optionally substituted 2H-chromenyl group. G1 denotes oxygen atom, carbonyl group, ethynyl group, group -NR3CO-, group -NR4-, group -NR5SO2-, group -SO2NR6-, group -CONR7-, group -C(=CHR8)- or group -CR9=CR10- (wherein, R3, R4, R5, R6 and R7 denote hydrogen atom, hydroxy group or optionally substituted alkyl group, R8 denotes cyano group, carboxyl group or optionally substituted alkoxycarbonyl group. R9 and R10

each independently denote hydrogen atom, halogen atom, optionally substituted alkyl group, optionally substituted cycloalkyl group, optionally substituted aryl group or a ring formed by linking R9 and R10 together), G2 denotes optionally substituted phenyl group, optionally substituted pyridyl group, optionally substituted thiazolyl group, optionally substituted isoxazolyl group, optionally substituted thienyl group, optionally substituted pyrimidinyl group, group -CHR11-CHR12- or group -CR13=CR14-(CR15=CR16) y- (wherein, in the formula R11 and R12 denote a ring formed by linking together, R13, R14, R15 and R16 each independently denote hydrogen atom, halogen atom, optionally substituted alkyl group, optionally substituted aryl group, a ring formed by linking R13 and R14 or R15 and R16 together, and y denotes an integer of 0-3), m and n each independently denote an integer of 0 or 1. Q denotes a group represented by (sic) carboxyl group, optionally substituted alkoxycarbonyl group, -CONH-(5-tetrazolyl) group, optionally substituted 5-tetrazolyl group, optionally substituted 1,2,3-triazolyl group, optionally substituted 2,4-dioxo thiazolidine-5-ylidenyl group, optionally substituted 4-oxo-2-thioxo thiazolidine-5-ylidenyl group, optionally substituted 5-oxo-4-tetrazolyl group, optionally substituted 3-(5-oxo)-(1,2,4) oxadiazolidinyl group, optionally substituted 2-(3,5-dioxo)-(1,2,4) oxadiazolinyl group, optionally substituted 5-(3-oxo)-(1,2,4) oxadiazolidinyl group or optionally substituted 3-(5-oxo)-iso oxazolidyl group).
(Wherein, the case in which m and n are 0 and Q is carboxyl group or alkoxycarbonyl group is excluded.)

Claim 2

A compound in accordance with Claim 1 or 2 (sic) and salts thereof, wherein R1 in formula (1) is hydrogen atom.

Claim 3

A compound in accordance with any one of the Claims 1-3 (sic) and salts thereof, wherein R2 in formula (1) is optionally substituted alkyl group or optionally substituted cycloalkyl group.

Claim 4

A compound in accordance with any one of Claims 1-4 (sic) and salts thereof, wherein A in formula (1) is optionally substituted phenyl group.

Claim 5

A compound in accordance with any one of Claims 1-4 and salts thereof, wherein a group represented by A in formula (1) is phenyl group, and 2-ethinyl thiazolyl group and a group represented by (G1)m-(G2)n-Q are meta configuration.

Claim 6

A compound in accordance with any one of Claims 1-5 and salts thereof, wherein Q in formula (1) is 5-tetrazolyl group.

Claim 7

A compound in accordance with any one of Claims 1-6 and salts thereof, wherein m and n in formula (1) is 0.

Claim 8

A compound in accordance with any one of Claims 1-6 and salts thereof, wherein m and n in formula (1) is 1, G1 is -NR3CO- and G2 is phenyl group which may have one or more substituents.

Claim 9

A compound in accordance with any one of Claims 1-6 or Claim 8 and salts thereof, wherein G2 in formula (1) is phenyl group which may have one or more substituents, and G1 and Q are para configuration.

Claim 10

A drug formed from a compound in accordance with any one of Claims 1-9 or salts thereof.

Claim 11

A drug for prevention and/or therapy of allergic disease containing as effective ingredient a compound in accordance with any one of Claims 1-9 or salts thereof.

Claim 12

A drug for prevention and/or therapy of disease participating leukotriene, containing as effective ingredient a compound in accordance with any one of Claims 1-9 or salts thereof.

Claim 13

A drug for prevention and/or therapy of disease participating histamine, containing as effective ingredient a compound in accordance with any one of Claims 1-9 or salts thereof.

Detailed Description of the Invention

(0001)

Technical Sphere of the Invention

This invention relates to the following, namely, ethinyl thiazoles useful as effective ingredient of

drug having bioactivity such as antiallergy action or the like.

(0002)

Technology of the Prior Art

Bronchial asthma which is classified into an allergic disease is the disease characterised by the chronic inflammation of respiratory tract, and as this cause substance, it is known the participation of various chemical compound (inflammatory mediator) such as leukotriene (LTs), thromboxane A2 (TXA2), platelet activating factor (PAF), histamine, prostaglandin (PG) or the like. One of these inflamed mediator leukotriene species is thought one of the main factor participating in expression of allergic trachea and bronchus disease, allergic lung disease, allergic shock or various allergic inflammation (Proc. Natl. Acad. Sci. USA. 80 : 1712-1716, 1983). Moreover, peptide leukotriene (LTs) is an inflammatory mediator produced by metabolism of arachidonic acid, and leukotriene C4(LTC4), leukotriene D4(LTD4) and leukotriene E4(LTE4) are known (Science, 220 : 568-575, 1983).

(0003)

There are many reports about biologically active substance (receptor antagonist) combined to receptor of these leukotriene species and counteracted with leukotriene species (Chimia 46 : 304-311, 1992 and J. Med. Chem. 1996, 39 (14) 2629-2654). Moreover, clinical performance of leukotriene receptor antagonist 4-oxo-8-(4-(4-phenyl butoxy) benzoylamino)-2-(tetrazol-5-yl)-4H-1-benzopyran • hemihydrate (Pranlukast: Drugs of the Future 1988, 13, 317-320) is going to be reported [Journal of clinical and experimental medicine 164 (4) : 225-247, 1993; Immunopharmacology & therapy, 12 (2) : 116 (222)-118 (224), 1994; and Journal of clinical therapeutics & medicine 9 (S-1) : 71-107, 1993 and the like], and usefulness of these leukotriene receptor antagonists is going to be observed.

(0004)

On the other hand, mast cell, eosinophil, basophil and the like are production cell of the said inflammatory mediator, and carry out important role in pathosis of allergic trachea and bronchus disease, allergic lung disease, allergic shock or various allergic inflammation. In mast cell, one of the representative inflammatory cell, cell is activated by exposing in sensitised state (the state that IgE antibody with respect to antigen is combined to Fc receptor of cell surface) to antigen again, and as a result, chemical mediator such as histamine, LTC4 or the like is freed, and caused vascular permeability facilitation, telangiectasia, smooth muscle spasm and the like.

(0005)

As agent inhibiting this series of reaction, Disodium cromoglycate (DSCG) [The Merck Index,

the 9th edition 2585 (1976)] and 9-methyl-3-(1H-tetrazol-5-yl)-4H-pyrido (1,2-a) pyrimidin-4-on potassium salt (pemirolast potassium) (Kokai 54-36294) and the like are known. Antiallergic drug is classified into the basic antiallergic drug having antihistaminic action and acidic antiallergic drug which does not have this action, and pemirolast potassium is a representative example of acidic antiallergic drug. Because acidic antiallergic drug does not have antihistaminic action, it is characterised by having no side effect such as feeling og mouth dryness, drowsiness or the like, and it is reported some effectiveness with respect to bronchial asthma and allergic rhinitis [Gendai iryo, 26 (7) 137 (2143)-139 (2145), 1994; Gendai iryo, 26 (7) 251 (2257)-255 (2261), 1994 and Progress in Medicine, 13 (10), 137 (2247)-147 (2257), 1993]. However, although these agents can be applied for bronchial asthma, there is a problem that the clinical satisfactory degree is not so high.

(0006)

Problems to be Overcome by this Invention

As the reason why aforesaid antiallergic drug is not satisfied clinically, it is nominated that causal substance induced an allergic disease (inflammatory mediator) is different by each person, and plurality of causal substance is participating simultaneously in many cases, and the diagnosis technique specifies the causal substance thereof is generally complicated. Accordingly when prevention and treatment of allergic disease is carried out using anti-allergy agent, it is anticipated to be useful in prevention and treatment of wide-ranging allergic disease the agent which simultaneously displays plurality of antiallergy action more than agent having single action as prior art antiallergic drug. Moreover, by administering a single agent having plurality of action in this way, there is a possibility to avoid the problems such as lowering of medical economy, expression of various side effect or attenuation of action due to drug interaction or the like in simultaneous administration of the plurality agent.

(0007)

More particularly it anticipates if it is possible to put forward a compound combining antagonism with respect to the leukotriene confirmed the clinical therapy and/or prevention effect and release inhibitory action of mediator such as histamine or the like, therapy and/or prevention of more wide-ranging allergic disease becomes possible. Accordingly the object of this invention is putting forward a drug for the prevention and/or therapy of allergic disease represented by bronchial asthma and as a further embodiment, to put forward a compound useful as effective ingredient of drug for the prevention and/or therapy of allergic disease co-having leukotriene antagonism and histamine release inhibitory action from mast cell.

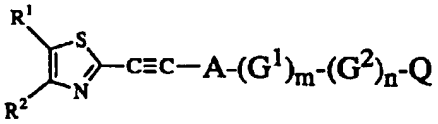
(0008)

Means to Overcome these Problems

These inventors carried out assiduous investigations in order to achieve the aforesaid problems. As a result, discovered that ethinyl thiazoles represented by the following formula has action combining leukotriene antagonism and histamine release inhibitory action from mast cell and aforesaid two actions could be expressed simultaneously and continuously by administering orally the said compound. This invention was completed on the basis of the said discovery.

(0009)

In other words, this invention is to put forward compound represented by general formula (1) and salts thereof



(1)

[wherein, R1 and R2 each independently denote hydrogen atom, halogen atom, optionally substituted alkyl group, optionally substituted cycloalkyl group, or a ring formed by linking R1 and R2 together. A denotes optionally substituted phenyl group, optionally substituted pyridyl group, optionally substituted furyl group, optionally substituted thienyl group, optionally substituted benzofuranyl group, optionally substituted benzo (b) thienyl group, optionally substituted benzoxazolyl group, optionally substituted benzothiazolyl group, optionally substituted pyrido (1,2-a) pyrimidinyl group, optionally substituted quinazolinyl group, optionally substituted benzo triazinyl group or optionally substituted 2H-chromenyl group. G1 denotes oxygen atom, carbonyl group, ethynyl group, group -NR3CO-, group -NR4-, group -NR5SO2-, group -SO2NR6-, group -CONR7-, group -C(=CHR8)- or group -CR9=CR10- (wherein, R3, R4, R5, R6 and R7 denote hydrogen atom, hydroxy group or optionally substituted alkyl group, R8 denotes cyano group, carboxyl group or optionally substituted alkoxycarbonyl group. R9 and R10 each independently denote hydrogen atom, halogen atom, optionally substituted alkyl group, optionally substituted cycloalkyl group, optionally substituted aryl group or a ring formed by linking R9 and R10 together), G2 denotes optionally substituted phenyl group, optionally substituted pyridyl group, optionally substituted thiazolyl group, optionally substituted isoxazolyl group, optionally substituted thienyl group, optionally substituted pyrimidinyl group, group -CHR11-CHR12- or group -CR13=CR14-(CR15=CR16) y- (wherein, in the formula R11 and R12 denote a ring formed by linking together, R13, R14, R15 and R16 each independently denote hydrogen atom, halogen atom, optionally substituted alkyl group, optionally substituted aryl group, a ring formed by linking R13 and R14 or R15 and R16 together, and y denotes an integer of 0-3), m and n each independently denote an integer of 0 or 1. Q denotes a group represented by (sic) carboxyl group, optionally substituted alkoxycarbonyl group, -CONH-(5-tetrazolyl) group,

optionally substituted 5-tetrazolyl group, optionally substituted 1,2,3-triazolyl group, optionally substituted 2,4-dioxo thiazolidine-5-ylidenyl group, optionally substituted 4-oxo-2-thioxo thiazolidine-5-ylidenyl group, optionally substituted 5-oxo-4-tetrazolyl group, optionally substituted 3-(5-oxo)-(1,2,4) oxadiazolidinyl group, optionally substituted 2-(3,5-dioxo)-(1,2,4) oxadiazolinyl group, optionally substituted 5-(3-oxo)-(1,2,4) oxadiazolidinyl group or optionally substituted 3-(5-oxo)-iso oxazolidyl group)].
(Wherein, the case in which m and n are 0 and Q is carboxyl group or alkoxycarbonyl group is excluded.)

(0010)
According to the preferred embodiment of the aforesaid invention, putting forward the aforesaid compound wherein R1 in formula (1) is hydrogen atom and salts thereof; the aforesaid compound wherein R2 in formula (1) is optionally substituted alkyl group or optionally substituted cycloalkyl group and salts thereof; the aforesaid compound wherein A in formula (1) is optionally substituted phenyl group and the salts thereof; the aforesaid compound wherein a group represented by A in formula (1) is phenyl group and a group represented by 2-ethinyl thiazolyl group and (G1)m-(G2)n-Q is in meta configuration, and salts thereof; the aforesaid compound wherein Q in formula (1) is 5-tetrazolyl group and salts thereof; the aforesaid compound wherein m and n in formula (1) is 0 and salts thereof; the aforesaid compound wherein m and n in formula (1) are 1 and G1 is -NR3CO- and G2 is phenyl group optionally having 1 or 2 or more substituents and the salts thereof; and the aforesaid compound wherein G2 in formula (1) is phenyl group optionally having 1 or 2 or more substituents and G1 and Q are para configurations, and the salts thereof.

(0011)
According to another embodiment of this invention, it is put forward drug comprising the said compound or salts thereof and drug for the prevention and/or therapy of allergic disease containing as effective ingredient the aforesaid compound or salts thereof as preferred embodiment thereof. Moreover, it is put forward drug for the prevention and/or therapy containing as effective ingredient the aforesaid compound or salts thereof for disease participated in leukotriene, preferably the allergic disease participated in leukotriene; and drug for the prevention and/or therapy wherein the aforesaid disease is an allergic disease originating in hyperexpression of leukotriene. Moreover, it is put forward the aforesaid drug for the prevention and/or therapy containing as effective ingredient the aforesaid compound or salts thereof for a disease participated in histamine, preferably the allergic disease participated in histamine; and drug for the prevention and/or therapy wherein the said disease is allergic disease originated in hyperexpression of histamine.

(0012)

Moreover, it is put forward drug containing as effective ingredient the aforesaid compound or salts thereof, for the prevention and/or therapy for a disease participated in leukotriene and histamine, preferably the allergic disease participated in leukotriene and histamine; and drug for the prevention and/or therapy wherein the said disease is allergic disease originated in hyperexpression of leukotriene and histamine. Moreover, according to the another embodiment of this invention, it is therapy and/or prevention process of a disease participated in leukotriene and histamine, preferably the allergic disease participated in leukotriene and histamine wherein process including step to administer to mammal animal including a human substance selected from the aforesaid compound or salts thereof in an effective dose; and aforesaid compound or salts thereof for production of therapy and/or preventative agent of the aforesaid allergic disease are put forward.

(0013)

Conditions for Carrying out this Invention

As "alkyl group" in this specification, for example, straight or branched chain saturated hydrocarbons of carbon number 1-12 is denoted, and for example, "cycloalkyl group" denotes 3-8 membered cyclic alkyl group. Moreover, term of "halogen atom" is used as concept including any of fluorine atom, chlorine atom, bromine atom and iodine atom untill otherwise particular mentioned. As ideal "alkoxyl group", for example, it is possible to use straight or branched chain alkoxyl group of carbon number 1-12.

(0014)

R1 and R2 each independently denote hydrogen atom, halogen atom, optionally substituted alkyl group, optionally substituted cycloalkyl group or ring formed by linking R1 and R2 together. As alkyl group, preferably it is possible to use straight or branched chain alkyl group of carbon number 1-8, more preferably straight or branched chain alkyl group of carbon number 1-5. In an embodiment, for example, methyl group, ethyl group, propyl group, isopropyl group, normal butyl group, isobutyl group, tertiary butyl group, pentyl group or the like such can be used. As substituent combined to the aforesaid alkyl group, for example, 1 or 2 or more substituents, preferably one substituent selected from the halogen atom, phenyl group, methoxyphenyl group, halogenophenyl group, benzyl group, methoxybenzyl group, dimethoxybenzyl group or halogeno benzyl group may be proposed. As far as halogenophenyl group is concerned, chlorophenyl group, and as halogeno benzyl group, chloro benzyl group or the like can be used.

(0015)

As the cycloalkyl group denoted by R1 and R2, it is possible to use preferably 3-5C cycloalkyl group, for example cyclopropyl group, cyclobutyl group and cyclopentyl group. As substituent combined to the aforesaid cycloalkyl group, for example, halogen atom may be proposed. As ring formed by linking R1 and R2 together, 5-8 membered ring, preferably 6 or 7 membered ring can be nominated, and it is possible to use for example cyclohexane ring, benzene ring or cycloheptane ring. As a combination of R1 and R2, it is preferred the case that R1 is hydrogen atom, and R2 is optionally substituted alkyl group or optionally substituted cycloalkyl group.

(0016)

A denotes an optionally substituted phenyl group, optionally substituted pyridyl group, optionally substituted furyl group, optionally substituted thienyl group, optionally substituted benzofuranyl group, optionally substituted benzo (b) thienyl group, optionally substituted benzoxazolyl group, optionally substituted benzothiazolyl group, optionally substituted pyrido (1, 2-a) pyrimidinyl group, optionally substituted quinazolinyl group, optionally substituted benzo triazinyl group or optionally substituted 2H-chromenyl group. As far as substituent is concerned, it is possible to use 1 or 2 or more, preferably one halogen atom. Preferably A is optionally substituted phenyl group.

(0017)

G1 denotes an oxygen atom, carbonyl group, ethynyl group, group -NR3CO-, group -NR4-, group -NR5SO_2-, group -SO_2NR6-, group -CONR7-, group-(C = CHR8- or group -CR9 = CR10-. Among these, group -NR3CO- is preferred. In the aforesaid group, R3, R4, R5, R6 and R7 each independently denote a hydrogen atom, hydroxy group or optionally substituted alkyl group. As alkyl group, preferably it is possible to use 1-8C straight or branched chain alkyl group, more preferably straight or branched chain alkyl group of carbon number 1-5. For example, methyl group, ethyl group, propyl group, isopropyl group, normal butyl group, isobutyl group or pentyl group can be used. For example, the aforesaid alkyl group may contain 1 or more substituents, preferably one substituent selected from the halogen atom, optionally substituted phenyl group, carboxyl group or alkoxycarbonyl group. It is preferred that R3, R4, R5, R6 and R7 are each independently hydrogen atom.

(0018)

R8 denotes cyano group, carboxyl group or optionally substituted alkoxycarbonyl group. As alkoxycarbonyl group, methoxycarbonyl group, ethoxycarbonyl group or 4-methoxybenzyl carbonyl group may be proposed. R9 and R10 each independently denote a hydrogen atom, halogen atom, optionally substituted alkyl group, optionally substituted cycloalkyl group, optionally substituted aryl or ring formed by linking R9 and R10 together. As cycloalkyl group, it

is possible to use preferably 3-5C cycloalkyl group, for example cyclopropyl group, cyclobutyl group and cyclopentyl group. As substituent combined to the aforesaid cycloalkyl group, for example, halogen atom may be proposed. As ring formed by linking R9 and R10 together, 5-8 membered ring, preferably 6 or 7 membered ring can be nominated, and for example, it is possible to use cyclohexane ring, benzene ring or cycloheptane ring. As far as aryl is concerned, phenyl group or the like can be used, and for example, as substituent on aryl group, it is possible to use halogen atom. Preferably R9 and R10 are hydrogen atom.

(0019)

G2 denotes an optionally substituted phenyl group, optionally substituted pyridyl group, optionally substituted thiazolyl group, optionally substituted isoxazolyl group, optionally substituted thienyl group, optionally substituted pyrimidinyl group, group -CHR11-CHR12- or group -CR13=CR14-(CR15=CR16) y-. The number of substituent existing in the aforesaid phenyl group or the like is not restricted in particular, and 1 or more than 2 substituents may be present. In particular, about the aforesaid phenyl group, there is the case it is preferably 2 or more substituents are present. For example, such substituent is selected from the halogen atom, nitro group, optionally substituted amino group, optionally substituted alkyl group, optionally substituted alkenyl group, optionally substituted alkynyl group, hydroxy group, optionally substituted alkoxyl group, optionally substituted alkyl or arylthio group, optionally substituted alkyl or aryl sulphonyl group, optionally substituted alkyl or arylsulfinyl group, carboxyl group or optionally substituted alkoxycarbonyl group or the like. As ring formed by linking R11 and R12 together, for example, cyclic alkyl group of 3-6C can be nominated, and as embodiments it is possible to ideally use cyclopropane ring, cyclopetane ring, cyclohexane ring or cyclohexene ring or the like.

(0020)

In the aforesaid group, R13, R14, R15 and R16 each independently denote hydrogen atom, halogen atom, optionally substituted alkyl group or optionally substituted aryl group, ring formed by linking together R13 and R14 or R15 and R16. Preferably R13 and R14 are hydrogen atom, halogen atom or optionally substituted alkyl group, and R15 and R16 are preferred to be hydrogen atom. As ring formed by linking together R13 and R14 or R15 and R16, cyclopropane ring, cyclopetane ring, cyclopentene ring, cyclohexane ring or cyclohexene ring or the like may be proposed. y denotes an integer of 0-3 and is preferably 0 or 1.

(0021)

In formula (1), m and n denote an integer of 0 or 1. When m and /or n denote 0, G1 and/or G2 denote single bond. Q denotes a carboxyl group, optionally substituted alkoxycarbonyl group, -

CONH-(5-tetrazolyl) group, optionally substituted 5-tetrazolyl group, optionally substituted 1,2,3-triazolyl group, optionally substituted 2,4-dioxo thiazolidine-5-ylidenyl group, optionally substituted 4-oxo-2-thioxo thiazolidine-5-ylidenyl group, optionally substituted 5-oxo-4-tetrazolyl group, optionally substituted 3-(5-oxo)-(1,2,4) oxadiazolidinyl group, optionally substituted 2-(3,5-dioxo)-(1,2,4) oxadiazolinyl group, optionally substituted 5-(3-oxo)-(1,2,4) oxadiazolidinyl group or optionally substituted 3-(5-oxo)-iso oxazolidyl group. Among these, 5-tetrazolyl group is preferred.

(0022)

As for R1 and R3 in compound of formula (1), it is preferred to be hydrogen atom. Preferably A is phenyl group, and preferably 2-ethinyl thiazolyl group and group-(G1)m-(G2)n-Q are combined in meta configuration through A. Q is preferred to be 5-tetrazolyl group. When m is 1, G1 is preferably group -NR3CO-, and when n is 1, it is preferred that G2 is phenyl group. When G2 denotes phenyl group, one substituent or two or more substituents may be presented on phenyl group, and when two or more substituents are present, they may be the same or different. As substituent on phenyl group, it can be used for example, halogen atom such as fluorine atom, chlorine atom or the like; alkyl group alkenyl group or alkynyl group such as methyl group, ethyl group, propyl group, n-butyl group, isobutyl group, hydroxymethyl group, acetoxymethyl group, 1-propenyl group, 2-propenyl group, ethynyl group or 1-propynyl group and the like; alkoxyl group such as ethoxyl group, n-propoxyl group, n-butoxyl group, isobutoxyl group, 2-fluoro ethoxyl group, 2,2,2-trifluoro ethoxyl group, phenoxyl group, benzyloxy group and the like; alkylthio group such as ethylthio group, n-propylthio group, butylthio group, benzylthio group, 2-hydroxyethyl thio group or the like, and alkylsulfonyl group obtained by oxidising sulfur atom of these alkylthio group; alkylamino group such as methylamino group, n-butylamino group and the like.

(0023)

Cyclobutyl, isopropyl, tert-butyl or cyclopropyl group are preferably as R2. When A is phenyl group containing substituent, as far as said substituent is concerned, fluorine atom is preferred. When A and G2 respectively denote phenyl group containing subsituent, it is needless to say that compounds obtained by combining substituents on each phenyl group in various ways are all included in a range of the compound of this invention.

(0024)

As preferred compound of this invention, compound such as 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole, 5-(3-(2-(4-isopropyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole, 5-(3-(2-(4-cyclopropyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole, 5-(3-(2-(4-n-propyl-2-thiazolyl)

ethinyl) phenyl)-1H-tetrazole, 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-fluorophenyl)-1H-tetrazole, 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-fluorophenyl)-1H-tetrazole 5-(3-(2-(4-isopropyl-2-thiazolyl) ethinyl)-2-fluorophenyl)-1H-tetrazole, 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylphenyl)-1H-tetrazole, 5-(3-(2-chloro-2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole, 5-(4-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-thienyl)-1H-tetrazole, 5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-3-pyridyl)-1H-tetrazole, 5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-benzoxazolyl)-1H-tetrazole, 5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-benzo (b) thienyl)-1H-tetrazole, 5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-oxo-2H-benzopyran-3-yl)-1H-tetrazole and 3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4H-(1,2,4)-oxadiazole-5-on and the like may be proposed.

(0025)

Moreover, as furthermore preferred compound, the compound wherein in formula (1), m and n are 1, and A and G2 are phenyl group, for example N-(4-(1H-tetrazol-5-yl) phenyl-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide, N-(3-(1H-tetrazol-5-yl) phenyl-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide, N-(2-methoxy-4-[1H-tetrazol-5-yl] phenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide, N-(2-methyl-4-[1H-tetrazol-5-yl] phenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide, N-(2-fluoro-4-[1H-tetrazol-5-yl] phenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-3-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl)-6-fluorophenyl)-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl)-6-fluorophenyl)-2-fluoro-4-(1H-tetrazol-5-yl) benzamide. N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-3-methyl-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-3-methoxy-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-tert-butyl-2-thiazolyl] ethinyl) phenyl)-2-fluoro-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-2-chloro-4-(1H-tetrazol-5-yl) benzamide. N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-2-methyl-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-2-methoxy-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-2-methylthio-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-2-amino-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-4-(1H-tetrazol-5-yl)-2-vinyl benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-4-(1H-tetrazol-5-yl)-2-trifluoromethoxy benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-2-hydroxy-4-(1H-tetrazol-5-yl) benzamide. N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-2,6-difluoro-4-(1H-tetrazol-5-yl) benzamide and N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-2,6-methyl-4-(1H-tetrazol-5-yl) benzamide and the like may be proposed. The compound wherein cyclobutyl group which is R2 moiety of the aforesaid compound is substituted to cyclopropyl group, isopropyl group, tert-butyl group or the like is also preferred compound of this invention.

(0026)

Moreover, as the compound which can be produced in the same way, for example N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl)-6-fluorophenyl)-2-chloro-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl)-6-fluorophenyl)-2-hydroxy-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl)-6-fluorophenyl)-2-methyl-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl)-6-fluorophenyl)-2-methylthio-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl)-6-fluorophenyl)-2-methylsulfinyl-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl)-6-fluorophenyl)-2-methylamino-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl)-6-fluorophenyl)-2-amino-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl)-6-fluorophenyl)-2-butylamino-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl)-6-fluorophenyl)-2,6-dichloro-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-2-fluoro-6-hydroxy-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-2-fluoro-6-methylamino-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-2-amino-6-fluoro-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-2-butylamino-6-fluoro-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-2-fluoro-6-methylsulfinyl-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-2-fluoro-6-hydroxymethyl-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-2-(2-fluoro ethoxy)-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-2-(2,2,2-trifluoro) ethoxy)-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-2-methylsulfinyl-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-2-n-butylamino-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-2-(2-hyroroxyethyl(sic)) thio-4-(1H-tetrazol-5-yl) benzamide. N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-2-ethinyl-4-(1H-tetrazol-5-yl) benzamide, N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-2-(1-propenyl)-4-(1H-tetrazol-5-yl) benzamide and N-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl)-2-(2-propenyl)-4-(1H-tetrazol-5-yl) benzamide and the like may be proposed. The compound wherein cyclobutyl group which is R2 moiety of the aforesaid compound is substituted to cyclopropyl group, isopropyl group, tert-butyl group or the like is also the compound which can be synthesised.

(0027)

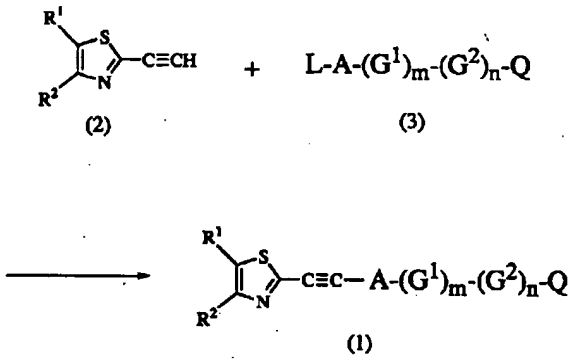
There is case that the compound of this invention represented by formula (1) contains 1 or two or more asymmetric carbons depending on the kind of substituent. However, the optically pure arbitrary isomer on the basis of 1 or more asymmetric carbons, the mixture of arbitrary optical

isomer or the racemic body are all included in the limit of this invention. Moreover, arbitrary mixture of diastereoisomer on the basis of 2 or more asymmetric carbons is also included in the limit of this invention. Moreover, for example, there is the case to present tautomer in the compound of this invention having tetrazole group or the like, however, it should understand that each tautomer or those arbitrary mixtures too are all included in the limit of this invention. There is case that the compound of this invention forms acid addition salt or base addition salt depending on the kind of substituent, and moreover, there is the case that free form compound or compound of a form of salts thereof is present as hydrate or solventate, however, all these are included in the limit of this invention.

(0028)

For example, the compound of this invention can be synthesised according to the following [Scheme 1]-[Scheme 8]. The compound represented by formula (1), as shown in Scheme 1, can be produced by coupling reaction of ethinyl thiazoles (2) and compound of formula (3) (in Schemes, R1, R2, A, G1, G2, Q, m and n have the same aforesaid meanings, and L denotes polyfluoro sulphonyl alkoxyl group or leaving group of iodine, bromine or the like.

[Scheme 1]



(0029)

2-ethinyl thiazole (2) shown in [Scheme 1] can be produced by well known method. It is possible to produce compound of formula (1) by coupling 2-ethinyl thiazole (2) and compound (3) at a temperature in a range of 0°C-boiling point of solvent in suitable inert solvent, for example inert ether type solvent such as tetrahydrofuran, 1,2-dimethoxyethane or the like, organic amine system solvent such as triethylamine, diisopropylamine or the like or in inert polar solvent such as N,N-dimethylformamide or the like according to itself well known literature method. The reaction may be carried out in the absence or in the presence of triphenylphosphine and cuprous iodide, and palladium (2) acetate, tetrakis (triphenylphosphine) palladium (0) or bis (triphenylphosphine) palladium (2) dichloride may be added in an amount of catalytic quantity,

preferably 0.1-10 % mol approximately. The reaction can be carried out under airflow of inert gas such as nitrogen, argon or the like.

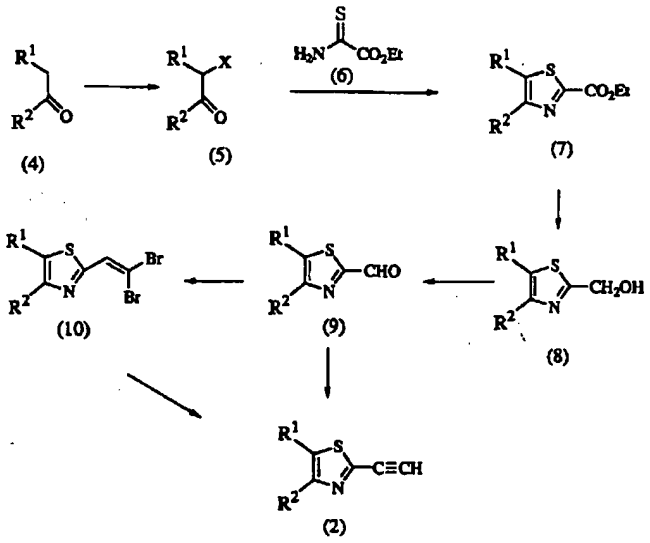
(0030)

In compound represented by formula (1), when Q is optionally substituted alkoxycarbonyl group, said compound can be converted to corresponding free carboxylic acid type compound by subjecting to acidify or alkali hydrolysis. Moreover, when Q is cyclic heterocyclic group, and protecting group such as substituted benzyl group or 2-(trimethylsilyl) ethoxymethyl group or the like is present as substituent in cyclic thereof, it is possible to produce the compound wherein Q is release form cyclic acidic group containing the acidic hydrogen atom by subjecting these compounds to well known deprotecting reaction. For example, when substituted benzyl group, 4-methoxybenzyl group are present as substituent, it is possible to eliminate substituted benzyl group and 4-methoxybenzyl group by carrying out the reaction in trifluoroacetic acid at a temperature in a range of 0°C-boiling point of solvent, preferably at room temperature-boiling point of solvent in the presence of the anisole or the like which is a scavenger of formed cation. Moreover, as for the compound having 2-(trimethylsilyl) ethoxymethyl group or the like on heterocycle as protecting group, it is possible to be eliminated the said protecting group by treating with tetra-n-butylammonium fluoride or cesium fluoride in inert ether type solvent such as tetrahydrofuran or the like. During this reaction, equivalent amount of acetic acid may be added.

(0031)

In the following [Scheme 2], the synthesis method of 2-ethinyl thiazole (2) used as raw material compound in the aforesaid reaction is shown (in Scheme, R1 and R2 have the same aforesaid meanings, and X denotes a chlorine atom or bromine atom).

[Scheme 2]



(0032)

2-thiazole esters (7) can be produced by reacting 2-halogenoketone species (5) [itself well known species or can be readily produced from compound (4) by a conventional method, or may possible to obtain commercial product] and commercially available thio amide [ethyl thio oxamate (6)] in an inert alcohol system solvent such as ethanol or the like or acetic acid at a temperature in a range of 0°C-boiling point of solvent. It is possible to convert ester body (7) to alcohol body (8) by well known reduction process. Reduction is possible to carry out by using reducing agent such as sodium borohydride or the like in a range of -20-50°C, preferably at 0°C-room temperature in inert alcohol system solvent such as ethanol or the like. Alcohol body (8) can be converted to aldehyde body (9) according to well known method to oxidize the primary hydroxy group into aldehyde. This oxidation reaction can be carried out for example, by oxidation using chromate species in inert halogenated hydrocarbon system solvent such as methylene chloride or the like in a range of -78°C-boiling point of solvent, preferably at -78°C-room temperature or by carrying out (Swern) oxidation, or by treating with active manganese dioxide in inert hydrocarbon solvent such as toluene or the like or in inert ketone system solvent such as acetone or the like at a temperature in a range of 0°C-boiling point of solvent, preferably at room temperature-boiling point of solvent.

(0033)

2-ethinyl thiazole (2) can be synthesised by the following process from aldehyde body (9). Using lithium diisopropyl amide or lithium hexamethyl disilazide as base, and trimethylsilyldiazomethane or diazomethane is treated in inert ether type solvent such as tetrahydrofuran or the like at -100°C to -20°C, preferably -50°C or less, and thereby carbanion of

diazomethane species is formed. 2-thiazole carbaldehyde (9) is added to solution including this carbanion preferably at temperature of -50°C or less and thereafter warmed to 0°C-room temperature, thereby transposition product 2-ethinyl thiazole (2) is possible to obtain.

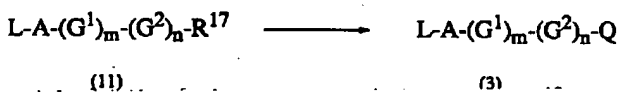
(0034)

As an alternate method, 2-ethinyl thiazole (2) may be synthesised as follows. According to process in accordance with literature, 2-thiazole carbaldehyde (9) is reacted with for example carbon tetrabromide and phosphorus reagent such as triphenylphosphine and the like in inert halogenated hydrocarbon system solvent such as methylene chloride or the like in a range of -20°C-boiling point of solvent, preferably at 0°C-room temperature, and thereby possible to obtain 1,1-dibromo-2-(2-thiazolyl) ethylene body (10). Thereafter, compound (10) is treated with 1.8-3 equivalents organic alkyllithium such as n-butyllithium or the like at a temperature in a range of -78°C-room temperature, preferably -78-0°C in inert ether type solvent such as tetrahydrofuran or the like, and thereafter, by neutralizing with diluted mineral acid such as diluted hydrochloric acid or the like or saturated ammonium chloride aqueous solution under low temperature in a range of -78-30°C, preferably 0°C or less, 2-ethinyl thiazole (2) can be obtained.

(0035)

The compound (3) used in [Scheme 1] can be synthesised as shown in [Scheme 3] by a process to convert to R17 of compound (11) to Q (in the scheme, A, G1, G2, Q, m, n and L have the same aforesaid meanings, and R17 denotes cyano group, formyl group, acetyl group, carboxyl group, carbamoyl group, hydrokyl(?) amino group or amino group)

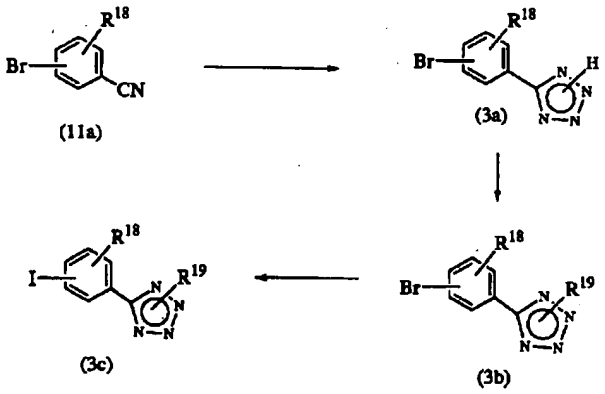
[Scheme 3]



(0036)

In the following [Scheme 3 A], as an illustration of reaction in accordance with "scheme 3", a process for the synthesis of compound (3b) wherein Q is tetrazolyl group containing 4-methoxybenzyl group or 2-(trimethylsilyl) ethoxymethyl group as protecting group from compound (11a) wherein A is phenyl group, m and n are 0, L is bromine atom, R17 is cyano groups, and a process for the synthesis of compound (3c) in which L is iodine atom are shown. (in the scheme, R18denotes hydrogen atom, halogen atom, nitro group, an alkyl group having substituents, an alkoxy group having substituents or alkoxycarbonyl group, and R19 denotes 4-methoxybenzyl group or 2-(trimethylsilyl) ethoxymethyl group).

[Scheme 3A]



(0037)

Benzonitrile body (11a) is itself well known or it can be produced using well known method, and tetrazole body (3a) can be produced from benzonitrile body (11a) according to well known reaction to convert cyano group into tetrazolyl group. For example, it is possible to obtain tetrazole body (3a) for example by treating benzonitrile body (11a) and aluminum azide or ammonium azide in inert polar solvent such as N,N-dimethylformamide or the like at a temperature range of room temperature-boiling point of solvent. The aluminum azide or ammonium azide used in the aforesaid reaction can be readily prepared according to well known method by treating sodium azide with quaternary ammonium salt such as aluminum chloride or ammonium chloride, pyridine hydrochloride or the like.

(0038)

A suitable protecting group is preferably introduced to the tetrazole body (3a) in order to carry out the next coupling reaction. As far as the protecting group is concerned, substituted benzyl group or 2-(trimethylsilyl) ethoxymethyl group described earlier is preferred. The reaction conditions for the introduction of protecting group are as follows. For example, tetrazole body (3a) is treated with 4-methoxybenzyl chloride or 2-(trimethylsilyl) ethoxymethyl chloride in inert polar solvent such as N,N-dimethylformamide or the like in the presence of inorganic base of for example potassium carbonate, at a temperature range of 0°C-boiling point of solvent, preferably room temperature to 80°C. In general, alkylation of tetrazolyl group gives mixture of 1-position substitution product and 2-position substitution product, but these can be separated by column chromatography using silica gel. Iodine atom is preferred as leaving group of compound (3), the compound (3c) can be obtained by converting bromine atom of compound (3b) into iodine atom according to well known method. For example, the compound (3c) can be produced by heating compound (3b) and cuprous iodide and potassium iodide in inert polar solvent such as N,N-dimethylformamide or the like preferably at a temperature range from 80°C to boiling point of solvent.

(0039)

In the following [Scheme 4], a process for the syntheiss of compound (3d) from compound (12) by completing G1 is shown. Moreover, in the following [Scheme 4A], a process for the syntheiss of compound (3d) wherein Q is 5-tetrazole group having 4-methoxybenzyl group or 2-(trimethylsilyl) ethoxymethyl group as protecting group from compound (12a) wherein A is phenyl group is shown (in the scheme, L, A, G1, G2 n, Q and R18 have the same the aforesaid meaning, and m is 1, and R20 denotes formyl group, acetyl group, carboxyl group, N-methoxy-N-methylcarbamoyl group, optionally substituted amino group, thiol group or chloro sulphonyl group, and R21 is 4-methoxybenzyl group).

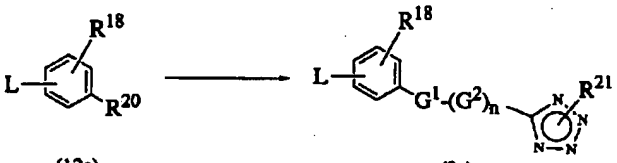
(0040)

[Shceme 4]

(12) (3d)

(0041)

[Shceme 4A]



(12a) (3e)

(0042)

In order to synthesise compound (3e) wherein G1 is group -CR9=CR10- (R9 and R10 have the same the aforesaid meanings) from benzaldehyde derivative or acetophenone derivative (12a) wherein R20 is formyl group or acetyl group, G1 is formed from the carbonyl group of benzaldehyde derivative or acetophenone derivative (12a) by Wittig reaction or Horner-Wadsworth-Emmons reaction, thereafter, the terminal cyano group is converted into tetrazolyl group in the same way, and 4-methoxybenzyl group or 2-(trimethylsilyl) ethoxymethyl group or the like is introduced as protecting group. Compound of formula (3e) wherein G1 is group -(C=O)- or group -(C=CHR8)-c an be synthesised from the compound (12a) wherein R20 is N-methoxy-N-methylcarbamoyl group (R8 has the same the aforesaid meaning).

(0043)

The compound (12a) wherein R20 is N-methoxy-N-methylcarbamoyl group can be readily

prepared by well known method from corresponding benzoyl chloride andcommercially available product, N,O-dimethyl hydroxylamine hydrochloride. This compound and 1-(4-methoxybenzyl)-1H-tetrazole produced by process described in the literature are treated with organic alkyllithium such as n-butyllithium or the like in inert ether type solvent such as tetrahydrofuran or the like at a temperature of range from room temperature to 100°C, thereafter this is neutralisation treated with dilute mineral acid such as dilute hydrochloric acid or the like or saturated ammonium chloride aqueous solution at low temperature, and thereby compound (3e) can be prepared. Moreover, it is possible to produce compound (3e) containing group -(C=CHR8)- by treating the carbonyl group of compound (3) using Horner-Wadsworth-Emmons reaction reagent or various kinds of Wittig reaction reagents.

(0044)

The compound (3e) wherein G1 is group -NR4- (R4 has the same the aforesaid meaning) can be produced by a process in which aniline derivative (12a) wherein R20 is optionally substituted amino group is converted to group -NR4-CN with cyanation reagent such as cyanogen bromide and the like, thereafter, tetrazol conversion of cyano group and introduction of protecting group are carried out the same way as above. Moreover, the compound (3e) wherein G1 is group -NR3CO- (R3 has the same the aforesaid meaning) can be produced by a process in which aniline derivative (12a) wherein R20 is optionally substituted amino group is condensed with cyano benzoyl chloride derivative optionally having substituent, thereby group -NR3CO- of G1 is formed, thereafter, tetrazol conversion of cyano group and introduction of protecting group are carried out the same way as above. Moreover, compound (3e) wherein G1 is group -NR5SO_2- (R5 has the same the aforesaid meaning) can be produced by a process in which aniline derivative (12a) wherein R20 is optionally substituted amino group is condensed with cyanobenzene sulphonyl chloride derivative optionally having substituent, thereby group -NR5SO_2- of G1 is formed, thereafter, tetrazol conversion of cyano group and introduction of protecting group are carried out the same way as above.

(0045)

The aniline derivative (12a) used by the aforesaid reaction is commercially available product or it can be readily produced by reduction of nitrobenzene derivative. Moreover, it can be produced by subjecting benzoic acid derivative to Curtius rearrangement reaction. For example, benzoic acid derivative and acid azide formation reagent such as diphenylphosphorylazide or the like are reacted in tert-butyl alcohol, or in a mixed solvent further combining inert aromatic hydrocarbon system solvent such as toluene or the like, in the presence of organic amine system base such as triethylamine or the like in a temperature range of 0°C to the boiling point of the solvent, preferably from room temperature to the boiling point of the solvent, thereby acylamino body

which is the Curtius rearrangement reaction resultsnt ccan be obtained. The said acylamino body is treated with acid such as hydrochloric acid or trifluoroacetic acid or the like, thereby aniline derivative (12a) can be derived.

(0046)

The alkylaniline derivative having optionally substituted alkyl group (mono substituted aniline, 12a) can be directly produced by reacting aniline derivative which is a primary amine with an active halide such as bromoacetic acid esters or the like in the presence of a base such as potassium carbonate and the like in inert polar solvent such as N,N-dimethylformamide or the like. Moreover, the aniline derivative which is a primary amine is trifluoproacetylated using anhydrous trifluoroacetic acid, thereafter, this is reacted with alkyl halide optionally having substituent, preferably iodo body in the presence of a base such as potassium carbonate and the like, furthermore, de-trifluoroacetylation is carried out and thereby the mono substituted aniline derivative (12a) can be produced. Moreover, N-hydroxyaniline derivative (12a) wherein R20 is optionally substituted alkyl group and the substituent thereof is hydroxy group can be prepared by carrying out zinc powder reduction of nitrobenzene derivative in the presence of ammonium chloride in water-containing ethanol.

(0047)

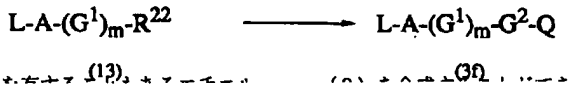
The compound (3a) wherein G1 is oxygen atom or sulfur atom can be synthesised from the benzenethiol derivative or phenol derivative (12a) wherein R20 is -OH or -SH. For example, aforesaid 1-(4-methoxybenzyl)-1H-tetrazole is treated in the co-presence of bromine or iodine with lithium diisopropyl amide or lithium hexamethyl disilazide at a temperature range of -100°C to room temperature, thereby 1-(4-methoxybenzyl)-1H-tetrazole derivative having bromine or iodine atom at 5-position can be produced. This 5-bromo- or 5-iodo-1-(4-methoxybenzyl)-1H-tetrazole is treated with benzenethiol derivative or phenol derivative (12a) in the presence of organic amine such as inorganic base or triethylamine or the like such as potassium carbonate or the like, in inert polar solvent such as N,N-dimethylformamide or the like and compound (3d) can be synthesised.

(0048)

In [Scheme 5], a scheme for synthesising composed compound (3f) by completing G2 from compound (13) is shown (in the scheme, L, A, G1, G2 m, Q and R18 have the same the aforesaid meaning, and n is 1, and R22 denotes optionally substituted ethynyl group, amino group, thiocarbamoyl group, bromoacetyl group or chloroacetyl group).

(0049)

[Scheme 5]



(0050)

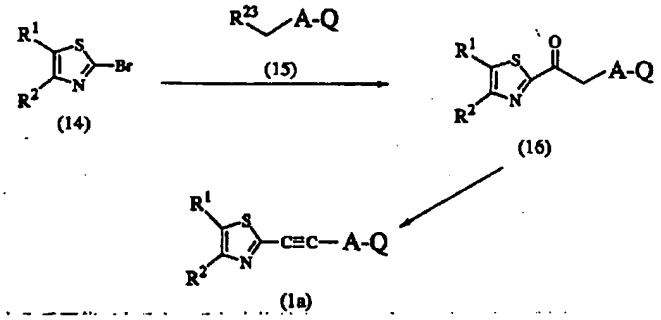
The compound (3) wherein G2 is isoxazolyl group can be synthesised from ethynylbenzene derivative (13) wherein R22 is optionally substituted ethynyl group and m is 0. The starting material compound ethynylbenzene derivative (13) can be produced from ethyl • propiolic acid and aryl halide, preferably iodobenzene derivative by coupling reaction using the aforesaid organopalladium (0-valent or divalent) catalyst. An alkyl nitro compound is treated with dehydrating agent such as phenyl isocyanate or the like in in inert hydrocarbon solvent such as toluene or the like or in inert ether type solvent such as tetrahydrofuran or the like, thereby nitrile oxide is formed, thereafter, the said nitrile oxide is reacted with the aforesaid ethynylbenzene derivative (13), thereby isoxazole derivative (3f) which is [2+3] cyclysation adduct can be produced. A compound (3f) wherein G2 is pyrimidinyl group can be produced from aniline derivative (13) wherein R22 is amino group and m is 0 by heating N-(carbomethoxy)-methoxymethylene acetamide derivative and aniline derivative (13) in high boiling point hydrocarbon solvent such as toluene or xylene or the like, preferably to a temperature range from 100°C to the boiling point of solvent, thereby forming pyrimidine ring, furhtermore by converting the cyano group to tetrazolyl group according to the aforesaid process.

(0051)

In [Scheme 6], as an illustration of process for the production of compound of formula (1) including triple bond moiety formation step, a scheme for the synthesis of ethinyl thiazole derivative (1a) wherein m and n are 0 by forming triple bond moiety from 2-bromothiazole derivative (14) is shown (in the scheme, R1, R2, A and Q have the same the aforesaid meanings, and R23 denotes an active amide such as alkoxycarbonyl group or N-methoxy-N-methylcarbamoyl group and the like).

(0052)

[Scheme 6]



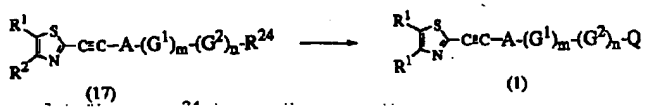
(0053)

2-bromothiazole derivative (14) which is commercial product or can be produced by itself commonly known or well known method (for example, it can be produced by bromination using Sandmeyer reaction via diazonium salt according to process in the literature from2-aminothiazole species which is easily obtained by dehydrocondensation of well known haloketone species and thiourea) is subjected to metal exchange reaction by treating with 1.8-3 equivalents of alkyllithium such as n-butyllithium or the like or Grinard reagnet such as methyl magnesium bromide or the like at a temperature range of -78°C to room temperature, preferably –78 to 0°C in inert ether type solvent such as tetrahydrofuran or the like, next it is reacted with compound (15) at low temperature, for example, a range of –78 to 30°C, preferably from 0°C to room temperature, thereafter, it is neutralised at a temperature of 0°C or less with dilute mineral acid such as dilute hydrochloric acid or the like or saturated aqueous ammonium chloride solution or the like, and thereby corresponding 2-(1-oxoethyl) thiazole (16) can be produced. Continuing, 2-(1-oxoethyl) thiazole (16) is dissolved in inert halogenated hydrocarbon system solvent such as 1,2-dichloro ethylene or the like, and triphenylphosphine oxide and trifluoromethane sulfonic acid anhydride are added at a temperature range of -10°C to room temperature, this mixture is reacted at a temperature range of10°C to the boiling point of solvent, preferably from room temperature to the boiling point of solvent, and thereby the target ethinylthiazole (1b) can be produced.

(0054)

In (scheme 7), a process to synthesise compound of formula (1) from compound (17) by completing Q is shown (in the scheme, R1, R2, A, G1, G2, m, n and Q have the same the aforesaid meanings, and R24 denotes formyl group, carboxyl group or cyano group).

[Scheme 7]



(0055)

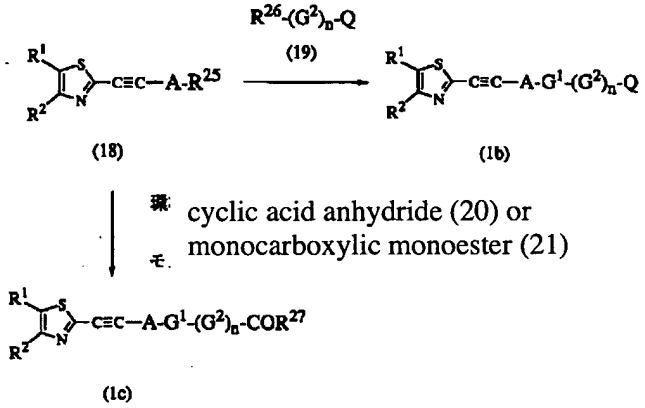
In order to produce compound (1) wherein Q is tetrazolyl group in accordance with (scheme 7) from compound (17) wherein R24 is cyano group, ethinylthiazole (2) and aryl halide are coupled according to the process shown in (scheme 1), thereby compound (17) wherein R24 is cyano group is produced, thereafter, this compound (17) is dissolved in inert polar solvent such as N,N-dimethylformamide or the like and this is treated with sodium azide in the presence of Lewis acid such as aluminum chloride or the like at a temperature range of 0°C to the boiling point of solvent, or treated with pyridine or trifluoroacetic acid salt of 6-lutidine or quaternary ammonium salt such as ammonium chloride or the like and sodium azide in a range of room temperature to the boiling point of solvent.

(0056)

The compound of formula (1) can aslo be produced by completing G1as shown in [Scheme 8] (in the scheme, R1, R2, n and Q have the same the aforesaid meanings, m is 1, R25 denotes carboxyl group or optionally substituted amino group, R26 denotes an amino group optionally having substitution, carboxyl group or chloro sulphonyl group, and R27 denotes hydroxy group or alkoxy group).

(0057)

[Scheme 8]



(0058)

In order to produce compound (1b) wherein G1 is -CONR4- (R4 has the same the aforesaid meaning) and Q is tetrazolyl group from benzoic acid derivative (18) wherein R25 is carboxyl group and A is phenyl group, iodo benzoate and ethinyl thiazole are coupled in accordance with coupling reacion shown in [Scheme 1], thereby benzoic acid derivative (18) is produced, furthermore, the alkali ester parts is hydrolysed, thereafter this is neutralisation treated with

addition of mineral acid such as hydrochloric acid or the like. This benzoic acid derivative (18) is reacted with amino body (19) wherein R 26 is amino group in inert halogenated hydrocarbon system solvent such as methylene chloride or the like, inert hydrocarbon solvent such as toluene or the like, inert ether type solvent such as tetrahydrofuran or the like or inert polar solvent such as N,N-dimethylformamide or the like, using condensing agent such as 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride N,N-dicyclohexylcarbodiimide, N,N-carbonyldiimidazole or analogues thereof, at a temperature range of -20°C to the boiling point of solvent, preferably 0°C to room temperature, thereby compound (1b) can be prepared.

(0059)

Moreover, as an alternative method, compound (18) is reacted with chlorinating agent such as thionyl chloride or the like or analogues thereof in inert hydrocarbon solvent such as toluene or inert halogenated hydrocarbon system solvent such as methylene chloride or the like in ar ange from room temperature to the boiling point of solvent, thereby acid chloride body of compound (18) can be prepared. This acid chloride body is reacted with amino derivative (19) which is a commercially available product or can be produced by well known method in inert halogenated hydrocarbon system solvent such as methylene chloride or the like, inert hydrocarbon solvent such as toluene or the like or inert ether type solvent such as tetrahydrofuran or the like, in accordance with requirements in the presence of organic base such as triethylamine or pyridine or the like or inorganic base such as sodium acetate or the like, at a temperature range of –10°C to the boiling point of solvent, preferably 0°C to room temperature, thereby it can be converted to corresponding compound (1d).

(0060)

The compound (1b) wherein G1 is group -NR3 CO- or group -NR5 SO_2- (R3 and R5 have the same the aforesaid meanings), n is 0 or when n is 1, G2 is phenyl group optionally substituted with 1 or 2 substituents, and also Q is tetrazolyl group can be produced from aniline derivative (18) wherein R24 is optionally substituted amino group and A is phenyl group. The aniline derivative (18) used as starting material compound can be produced from iodo-nitrobenzoic acid and ethinyl thiazole by carrying out the coupling reaction shown in [Scheme 1], thereafter by further reducing the nitrogr thereof using well known reducing agnet. When for example, stannous chloride or analogues thereof is used as reducing agent, the reaction can be carried out using inert·alcohol system solvent such as ethanol or the like, in a range of 0°C to the boiling point of solvent. Moreover, when metal such as tin, copper or the like is used as reducing agent, the reaction is carried out in diluted mineral acid such as dilute hydrochloric acid or the like or in a mixed solvent of mineral acid dilute hydrochloric acid or the like and ether system inert solvent such as dioxane or the like at a temperature range of 0°C to the boiling point of solvent, and on

completion of the reaction, the acidic solution is made weak alkaline, thereby aniline derivative (18) can be produced. The condensation reaction of aniline derivative (18) with 5-tetrazole carboxylic acid derivative (19) (when n is 0) or with benzoic acid derivative (19) (when n is 1) can be carried out in inert ether type solvent such as tetrahydrofuran or the like or inert polar solvent such as N,N-dimethylformamide or the like, using condensing agent such as 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride N,N-dicyclohexylcarbodiimide, N,N-carbonyldiimidazole or analogues thereof, at a temperature range of -10°C to the boiling point of solvent, preferably 0°C to room temperature, and in accordance with requirements, the reaction can be carried out in the presence of organic base such as triethylamine, 4-dimethylaminopyridine or the like or inorganic base such as sodium acetate or the like, and thereby corresponding compound (1b) can be obtained.

(0061)

As an alternative method, aniline derivative (18) is treated with acid chloride derived from 5-tetrazole carboxylic acid derivative (19) (when n is 0) or benzoic acid derivative (19) (when n is 1), thereby G1 of group -NR3 CO- is completed and it can be converted to compound (1b). Moreover, the compound (1b) wherein G1 is NR5 SO_2- can be obtained by condensing aniline derivative (18) with aryl sulphonyl chloride (19) which is itself well known or can be commercially available in inert halogenated hydrocarbon system solvent such as methylene chloride or the like, inert ether type solvent such as tetrahydrofuran or the like or inactivity polar solvent such as N,N-dimethylformamide or the like in the presence of organic amine species such as triethylamine or pyridine and the like.

(0062)

The compound (18) wherein R25 is optionally substituted amino group is acylated cyclic acid anhydride (20) which is commercial product or can be produced by well known method, and thereby compound (1c) can be produced. This is a process to synthesise G1, G2 and Q of compound (1c) in one go [G1 is group –NR3 CO-, G2 is group -CHR11-CHR12- or group -CHR13=CHR14-(CR15=CR16)y-, Q is carboxy group (R3, R11, R12, R13, R14, R15, R16 and y have the same meanings as above)]. This aniline derivative (18) and cyclic acid anhydride (20) are reacted in inert halogenated hydrocarbon system solvent such as methylene chloride or the like, inert hydrocarbon solvent such as toluene or the like or inert ether type solvent such as tetrahydrofuran or the like, in accordance with requirements in the presence of inert organic amine such as triethylamine or the like or inert inorganic base such as sodium acetate or the like at a temperature range of -10°C to the boiling point of solvent, thereafter, it is neutralised using mineral acid such as dilute hydrochloric acid or the like, and thereby corresponding compound (1c) can be obtained. As an alternative method, aniline derivative (18) and monocarboxylic acid

monoester species (21) are condensed in inert halogenated hydrocarbon system solvent such as methylene chloride or the like, inert ether type solvent such as tetrahydrofuran or the like or inert polar solvent such as N,N-dimethylformamide or the like, using condensing agent such as N,N-dicyclohexylcarbodiimide, N,N-carbonyldiimidazole or analogues thereof, at a temperature range of -20°C to the boiling point of solvent, preferably 0°C to room temperature, thereafter, ester hydrolysis is carried out and thereby compound (1c) can be produced.

(0063)

The compound of this invention represented by formula (1) is characterised by combining strong peptide leukotriene antagonism and release inhibitory action of mediator such as histamine or the like, and it is useful as an active ingredient for drug. Drug comprising the compound of this invention is useful therapeutically and/or preventatively for, for example various disease participating in leukotriene and/or histamine discharged from the mast cell, preferably various disease originating in excess expression of leukotriene and/or release repletion of histamine, for example bronchial asthma, lung anaphylaxis, cystic fibrosis, chronic bronchitis, bronchiectasis, respiration distress syndrome, lung edema, psoriasis, nephritis, allergic rhinitis or atopic dermatitis or the like. Moreover, it is also useful for therapy and/or prevention to brain edema and cerebral vasospasm like originating in cerebral ischemia, angina pectoris due to coronary blood flow decrease or hepatitis or the like.

(0064)

When the compound of this invention is used as a drug. other than compound of release form, compound in a form of the pharmacologically acceptable salt may be used. When compound of formula (1) contains acidic group such as 5-tetrazolyl group, carboxyl group and the like, base addition salt can be generally formed. As pharmacologically acceptable salt, any of organic salt species or inorganic salt species may be used, and as ideal example thereof, for example, alkali metal salt such as lithium salt, sodium salt, potassium salt or the like, alkaline earth metal salt such as magnesium salt, calcium salt or the like, ammonium salt, triethylamine salt, N-methyl glucamine salt or tris (hydroxymethyl) aminomethane salt may be proposed. Moreover, as drug of this invention, solventate or hydrates thereof may be used other than compound in release form or salt form.

(0065)

When compound of formula (1) or salts thereof or solventate or hydrates thereof is administered as drug to mammal including human, the substance itself may be administered, but usually it is preferred to administer by preparing medicinal composition including as an active ingredient said substance according to process well-known to a person skilled in the art. Such medicinal

composition can be administered aorally or orally and, besides substance of the said effective ingredient, it can be formulated effective ingredient of other drug, for example antihistamine, xanthine derivative, β irritant or antiasthmatic steroid (for example prednisolone and prednisoline). As example of medicinal composition suitable for oral administration, for example, tablet, powder, granule, fine granule, encapsulated formulation, suspending agent, solvent, syrup, elixir agent or the like may be proposed. As example of medicinal composition suitable for parenteral administration, for example, intravenous injection agent, drip infusion agent, suppository for endorectal administration, nasal drops, ear drops, locally external medicine such as ointment and cream agent or the like, percutaneous absorption agent, permucose membrane absorption agent, aerozol, fine pulverized powder, inhalant of a form of atomised solution or the like may be proposed.

(0066)

For example, talc, starch, milk sugar or other phusiologically acceptable carrier for the preparation can be used in production of medicinal composition suited for oral administration, and moreover, sugar or other edulcorant, flavor, coloring agent, binder or other drug additive may be used. In case of parenteral administration, it is possible to prepare solvent or suspending agent or the like using prior art generally used liquid vehicle, for example distilled water for injection, buffer, peanut oil or the like. When it is administered as aerozol, it is dissolved in suitable solvent which can be permitted phusiologically, for example ethanol or in a combination of miscibility solvent, and it can be mixed with phusiologically acceptable propellant. It is preferably to encapsulate medicinal composition for aerozol in the pressurized vessel fitted with the aerozol valve suitable for release of pressurised composition in order to use, and it is preferred the measure valve which can discharge medicinal composition of prescribed effective dosage by one movement is fitted to said container. Dosage regimen such as dose of drug of this invention and administration frequency or the like is not restricted in particular, and it can be suitably selected corresponding to titer and duration of activity of substance of the effective ingredient to be administered, administration pathway and severity, age or the like of animal comprising object of therapy and/or prevention. For example, dose of oral administration of medicinal composition including compound of formula (1) or salts thereof is in a range of about 0.1mg-2000mg, preferably about 0.1mg-500 mg as a quantity of effective ingredient per dose or dose divided into several times.

(0067)

Moreover, application of the compound of this invention is not restricted to the drug having itself drug activity, and is useful as synthesis intermediate and prodrug. For example, compound containing alkyl group, benzyl group, alkoxyalkyl group, and phenylalkyl group or the like as

substituent in the aforesaid acidic group moiety is useful as synthesis intermediate. Moreover, for example, compound containing acetoxymethyl group, pivaloyloxymethyl group, ethoxycarbonyl group, dimethylaminoethyl group or 5-indanyl group or the like in acidic group moiety as substituent can be used as prodrug.

(0068)

Examples

Hereinafter, it is described in greater detail using Example furthermore. However, these are in ones described in order to an illustration of this invention and the scope of this invention is not limited thereby. In the examples, (IR) (NMR) and (MS) each denote (infrared absorption spectrum) (nuclear magnetic resonance spectrum) and (mass spectrometry). Ratio of eluting solvent in separation by chromatography denotes volume ratio. (IR) was measured by KBr compression method. (NMR) denoted (1 H)-NMR, and solvent in parentheses denotes measurement solvent, and tetramethylsilane (TMS) was used as internal standard substance always. Moreover, as is common knowledge, for example 5-tetrazolyl group, 4-(1, 2,3)-triazolyl group and 5-(1, 2,3)-triazolyl group have mutually differing hydrogen atoms. For convenience, in these examplez these groups are respectively represented with 1H-tetrazol-5-yl, 1H-(1,2,3)-triazol-4-yl group and 1H-(1,2,3)-triazol-5-yl group).

(0069)

Reference Example 1

4-cyclobutyl-2-ethinyl thiazole =. (Step 1).

Synthesis of ethyl 4-cyclobutyl-2-thiazole carboxylate

Ethyl thioxamate 9 g and bromomethyl cyclobutyl ketone 11.96 g were heated under reflux for two hours in ethanol 70 ml. After cooling, the reaction liquor was concentrated. Methylene chloride 200 ml were added to the residue, and thereafter, was washed using saturated sodium bicarbonate and saturated aqueous sodium chloride solution. Methylene chloride layer was dried with anhydrous sodium sulphate, and thereafter, it was eliminated by distillation. Residual oily material was purified by column chromatography (eluate = n-hexane : ethyl acetate = 8 : 1) using silica gel, and 13.7g of ethyl 4-cyclobutyl-2-thiazole carboxylate was obtained as a straw-coloured oily substance.

NMR (400 MHz, CDCl3) δ ppm1.43 (3H, t), 1.88-2.44 (6H, m), 3.78 (1H, quint), 4.48 (2H, q), 7.23 (1H, s).

(0070).

(Step 2).

Synthesis of 4-cyclobutyl-2-thiazole methanol

Ethyl 4-cyclobutyl-2-thiazole carboxylate 13.7 g were dissolved in ethanol 60 ml, and sodium borohydride 2.45 g were gradually added under ice-cooling. The reaction liquor was stirred at room temperature furthermore for eight hours. Water was added to the reaction liquor while ice cooling and the excess sodium borohydride was decomposed and thereafter extraction was carried out with methylene chloride. The liquid extract was washed at saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate. the solvent was eliminated by distillation, and 4-cyclobutyl-2-thiazole methanol 8.39 g was obtained as pale-brown oily substance.

NMR (400 MHz, CDCl3) δ ppm1.85-2.43 (6H, m), 3.63 (1H, m), 3.77 (1H, br), 4.91 (2H, d), 6.86 (1H, s).

(0071).

(Step 3).

Synthesis of 4-cyclobutyl-2-thiazole carba aldehyde

Method a. Oxalyl 43.2 g dichloride was dissolved in methylene chloride 350 ml, and dimethyl sulphoxide (hereinafter, abbreviated to DMSO) 53.1 g was added dropwise by-70°C under stirring. On completion of the dropwise addition, it was stirred at the same temperature furthermore for 0 hours 30 minutes. Methylene chloride 100 ml solution of 4-cyclobutyl-2-thiazole methanol 28.8 g was added dropwise at the same temperature in this solution. On completion of the dropwise addition, also, after 1 hour, triethylamine 103 g were added. The reaction liquor was warmed to room temperature, and next water 100 ml were added, and it was extracted twice using ether 500 ml. The liquid extract was washed with saturated aqueous sodium chloride solution and thereafter was dried with anhydrous magnesium sulphate. the solvent was eliminated by distillation under reduced pressure, and the obtained residue was purified by column chromatography (eluate = n-hexane : ethyl acetate = 8 : 1) using silica gel, and 4-cyclobutyl-2-thiazole carba aldehyde 19.9 g were obtained as a straw-coloured oily substance.

(0072) Method b. 4-cyclobutyl-2-thiazole methanol 1.18 g and active manganese dioxide 1.21 g were heated under reflux for four hours in toluene 50 ml. After cooling, celite was used, and the insolubles were separated under reduced pressure by filtration. The filtrate was distilled under reduced pressure, and the obtained residue was purified by column chromatography (eluate = n-hexane : ethyl acetate = 8 : 1) using silica gel, and 4-cyclobutyl-2-thiazole carba aldehyde 800 mg was obtained as a straw-coloured oily substance.

NMR (400 MHz, CDCl3) δ ppm1.92-2.48 (6H, m), 3.76 (1H, m), 7.35 (1H, s), 9.99 (1H, s).

(0073)

Step 4

Synthesis of 1,1-dibromo-2-(4-cyclobutyl-2-thiazolyl) ethylene

Carbon tetrabromide 3.97 g were dissolved in methylene chloride 50 ml, and triphenyl phosphine 6.27 g were added at-10°C. Methylene chloride 5 ml solution of 4-cyclobutyl-2-thiazole carba aldehyde 1 g was added dropwise at the same temperature in this solution. On completion of the dropwise addition, the reaction liquor was returned to room temperature. Aqueous solution of saturated sodium bicarbonate was added to the reaction liquor, and it was neutralized, and thereafter, extraction was carried out with chloroform. The liquid extract was dried with anhydrous magnesium sulphate, and oily substance obtained by distilling off the solvent under reduced pressure was purified by column chromatography (eluate = n-hexane : ethyl acetate = 4 : 1) using silica gel, and 1,1-dibromo-2-(4-cyclobutyl-2-thiazolyl) ethylene 1.9 g were obtained as pale-brown oily substance.

NMR (400 MHz, CDCl3) δ ppm1.89-2.41 (6H, m), 3.68 (1H, m), 7.02 (1H, s), 7.95 (1H, s).

(0074)

Step 5

Synthesis of 4-cyclobutyl-2-ethinyl thiazole

Method a. 1,1-dibromo-2-(4-cyclobutyl-2-thiazolyl) ethylene 1.48 g were dissolved in tetrahydrofuran (hereinafter, abbreviated to THF) 20 ml, and n-butyllithium (n-hexane solution of 1.5M) 6.1 ml under stirring were added dropwise under a stream of nitrogen at-70°C. On completion of the dropwise addition, the reaction liquor was stirred at the same temperature furthermore for one hour. Saturated ammonium chloride aqueous solution 50 ml were added to the reaction liquor, and thereafter, it was returned to room temperature. The reaction liquor was extracted twice with ethyl acetate. The liquid extract was washed with saturated aqueous sodium chloride solution and thereafter was dried with anhydrous magnesium sulphate. The solvent was distilled off under reduced pressure, and an obtained oily substance was purified by column chromatography (eluate = n-hexane : ethyl acetate = 8 : 1) using silica gel, and 4-cyclobutyl-2-ethinyl thiazole 546 mg was obtained as pale-brown oily substance.

(0075) Method b. Diisopropylamine 10.1 g were dissolved in THF20ml, and n-butyllithium (n-hexane solution of 1.7M) 59 ml under stirring were added dropwise under a stream of nitrogen at-78°C. The reaction liquor was stirred at 0°C furthermore for 0 hours 30 minutes, and thereafter, cooled to 78°C again and 50ml of trimethylsilyldiazomethane (n-hexane solution of 2M) was added dropwise while holding at internal temperature-50°C or less. On completion of the dropwise addition, the reaction liquor was stirred at 78°C for 0.5 hours. While holding at internal temperature-50°C or less, solution in THF100ml of 4-cyclobutyl-2-thiazole carba aldehyde 15.8 g was dropwise aded. The reaction liquor was stirred at 78°C for one hour and thereafter, it was stirred at 0°C for one hour and also was stirred at room temperature for one hour. The reaction

liquor was discharged into 300ml of ice and saturated ammonium chloride aqueous solution and extraction was carried out with ethyl acetate. The liquid extract was washed with saturated aqueous sodium chloride solution and thereafter, was dried with sodium sulfate. An oily substance obtained by elimination by distillation of the solvent was purified by column chromatography (eluate = n-hexane : ethyl acetate = 8 : 1) using silica gel, and 4-cyclobutyl-2-ethinyl thiazole 11.1 g was obtained as pale-brown oily substance.
NMR (400 MHz, CDCl3) δ ppm1.88-2.38 (6H, m), 3.44 (1H, s), 3.67 (1H, m), 6.93 (1H, s).

(0076)

Reference Example 2

2-ethinyl benzothiazole =. Step 1. Synthesis of 2-(2,2-dibromo ethenyl) benzothiazole
Benzothiazole-2-carbaldehyde 2.00 g were treated in the same way as in Step 4 of Reference Example 1, and it was crystallised from the n-hexane, and 2-(2,2-dibromo ethenyl) benzothiazole 1.79 g was obtained as a crystalline powder.
mp. 102-103°C.
NMR (400 MHz, CDCl3) δ ppm7.44-7.48 (1H, m), 7.50-7.54 (1H, m), 7.90-7.92 (1H, m), 8.06 (1H, s), 8.06-8.08 (1H, m).

(0077)

Step 2

Synthesis of 2-ethinyl benzothiazole
2-(2,2-dibromo ethenyl) benzothiazole 1.75 g was treated in the same way as in method a of Step 5 of Reference Example 1, and product was purified by column chromatography (eluate = n-hexane : ethyl acetate = 10 : 1) using silica gel, and 2-ethinyl benzothiazole 0.63 g was obtained as pale-brown oily substance.
NMR (400 MHz, CDCl3) δ ppm7.45-7.49 (1H, m), 7.51-7.55 (1H, m), 7.86-7.88 (1H, m), 8.07-8.09 (1H, m).

(0078)

Reference Example 3

4-n-propyl-2-ethinyl thiazole:
4-n-propyl-2-carbaldehyde 1.36 g were treated in the same way as in b method of Step 5 of Reference Example 1, and product was purified by column chromatography (eluate = n-hexane : ethyl acetate = 10 : 1) using silica gel, and 4-n-propyl-2-ethinyl thiazole 0.73 g was obtained as pale-brown oily substance.
NMR (400 MHz, CDCl3) δ ppm0.96 (3H, t), 1.74 (2H, m), 3.44 (2H, t), 6.92 (1H, s).

(0079)

Reference Example 4

4-cyclopropyl-2-ethinyl thiazole:

4-cyclopropyl-2-carbaldehyde was treated in the same way as in b method of Step 5 of Reference Example 1, and 4-cyclopropyl-2-ethinyl thiazole 0.73 g was obtained as pale-brown oily substance.

NMR (400 MHz, CDCl3) δ ppm0.92-0.99 (4H, m), 2.01-2.08 (1H, m), 3.42 (1H, s), 6.88 (1H, s).

(0080)

Reference Example 5

4-isopropyl-2-ethinyl thiazole:

4-isopropyl-2-carbaldehyde was treated in the same way as in b method of Step 5 of Reference Example 1, and 4-isopropyl-2-ethinyl thiazole was obtained as pale-brown oily substance.

NMR (400 MHz, CDCl3) δ ppm1.32 (6H, d), 3.31 (1H, m), 3.44 (1H, s), 6.92 (1H, s).

(0081)

Reference Example 6

4-tert-butyl-2-ethinyl thiazole:

4-tert-butyl-2-carbaldehyde was treated in the same way as in b method of Step 5 of Reference Example 1, and 4-tert-butyl-2-ethinyl thiazole was obtained as an oily substance.

NMR (400 MHz, CDCl3) δ ppm1.36 (9H, s), 3.43 (1H, s), 6.94 (1H, s).

(0082)

Reference Example 7

4-isopropyl-5-methyl-2-ethinyl thiazole:

Isopropyl-5-methyl-2-carbaldehyde was treated in the same way as in b method of Step 5 of Reference Example 1, and 4-isopropyl-5-methyl-2-ethinyl thiazole was obtained as an oily substance.

NMR (400 MHz, CDCl3) δ ppm1.27 (6H, d), 2.38 (3H, s), 3.06 (1H, m), 3.39 (1H, s).

(0083)

Reference Example 8

4-cyclopentyl-2-ethinyl thiazole:

4-cyclopentyl-2-carbaldehyde was treated in the same way as in b method of Step 5 of Reference Example 1, and 4-isopropyl-2-ethinyl thiazole was obtained as pale-brown oily substance.

NMR (400 MHz, CDCl3) δ ppm1.60-2.70 (8H, m), 3.21 (1H, m), 3.43 (1H, s), 6.92 (1H, s).

(0084)

Reference Example 9

4-cyclohexyl-2-ethinyl thiazole.

4-cyclohexyl-2-carbaldehyde was treated in the same way as in b method of Step 5 of Reference Example 1, and 4-cyclopentyl-2-ethinyl thiazole was obtained as prism crystals.

mp. 77-78°C.

NMR (400 MHz, CDCl3) δ ppm1.20-2.10 (10H, m), 2.77 (1H, m), 3.42 (1H, s), 6.89 (1H, s),

MS(EI)m/z 191(M+), elemental analysis values C11H13NS

Theoretical value (%), C, 69.06, H, 6.85, N, 7.32,

Measured value (%), C, 68.91, H, 6.83,N, 7.14..

(0085)

Reference Example 10

4-(methylthio) methyl-2-ethinyl thiazole

4-(methylthio) methyl-2-carbaldehyde was treated in the same way as in b method of Step 5 of Reference Example 1, and 4-(methylthio) methyl-2-ethinyl thiazole was obtained as pale-brown oily substance.

NMR (400 MHz, CDCl3) δ ppm2.11 (3H, s), 3.47 (1H, s), 3.83 (2H, s), 7.18 (1H, s).

(0086)

Reference Example 11

4-methoxymethyl-2-ethinyl thiazole.

4-methoxymethyl-2-carbaldehyde was treated in the same way as in b method of Step 5 of Reference Example 1, and 4-methoxymethyl-2-ethinyl thiazole was obtained as pale reddish brown oily substance.

NMR (400 MHz, CDCl3) δ ppm3.47 (4H, s), 4.60 (2H, s), 7.27 (1H, s).

(0087)

Reference Example 12

4-methyl-2-ethinyl thiazole.

4-methyl-2-carbaldehyde was treated in the same way as in b method of Step 5 of Reference Example 1, and 4-methyl-2-ethinyl thiazole was obtained as pale-brown oily substance.

NMR (400 MHz, CDCl3) δ ppm2.47 (3H, s), 3.44 (1H, s), 6.92 (1H, s).

(0088)

Reference Example 13

4-isobutyl-2-ethinyl thiazole:

4-isobutyl-2-carbaldehyde was treated in the same way as in b method of Step 5 of Reference Example 1, and 4-isobutyl-2-ethinyl thiazole was obtained as pale-brown oily substance.
NMR (400 MHz, CDCl3) δ ppm0.92 (6H, d), 2.08 (1H, m), 2.64 (2H, d), 3.44 (1H, s), 6.90 (1H, s).

(0089)

Reference Example 14

4-ethyl-2-ethinyl thiazole:

4-ethyl-2-carbaldehyde was treated in the same way as in b method of Step 5 of Reference Example 1, and 4-ethyl-2-ethinyl thiazole was obtained as pale-brown oily substance.
NMR (400 MHz, CDCl3) δ ppm1.31 (3H, t), 2.82 (2H, q), 3.44 (1H, s), 6.92 (1H, s).

(0090)

Reference Example 15

4-n-octyl-2-ethinyl thiazole:

4-n-octyl-2-carbaldehyde was treated in the same way as in b method of Step 5 of Reference Example 1, and 4-n-octyl-2-ethinyl thiazole was obtained as pale yellow oily substance.
NMR (400 MHz, CDCl3) δ ppm0.87 (3H, t), 1.26-1.74 (12H, m), 2.77 (2H, t), 3.43 (1H, s), 6.90 (1H, s).

(0091)

Reference Example 16

4-cyclobutyl-2-(2-(3-nitrophenyl) ethinyl) thiazole:

10 ml of diisopropylamine were added to 3-iodo nitrobenzene 519 mg, cuprous iodide 40 mg, tetrakis (triphenyl phosphine) palladium (0) 120 mg, and 4-cyclobutyl-2-ethinyl thiazole 340 mg was added with stirring under a stream of nitrogen at room temperature. The reaction liquor was stirred at room temperature furthermore for one hour. Oily substance obtained when the reaction liquor was distilled under reduced pressure, was purified by column chromatography (eluate = n-hexane : ethyl acetate = 8 : 1) using silica gel, and 4-cyclobutyl-2-(2-(3-nitrophenyl) ethinyl) thiazole 502 mg was obtained as pale yellow fine needle crystal.
mp. 107-109°C.
IR ÉÀ max cm-11528.
NMR (400 MHz, CDCl3) δ ppm1.90-2.44 (6H, m), 3.71 (1H, quint), 7.02 (1H, s), 7.57 (1H, t), 7.89 (1H, t), 8.24 (1H, ddd), 8.44 (1H, t), MS(FAB)m/z 285 (M+ +1).

(0092)

Reference Example 17

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline:

4-cyclobutyl-2-(2-(3-nitrophenyl) ethinyl) thiazole 500 mg and stannic chloride (2 hydrate) 1.43 g were heated under reflux for two hours under stirring in ethanol 10 ml. After cooling, the solvent was eliminated by distillation. 4N sodium hydroxide aqueous solution was added under ice cooling to an obtained oily substance, and next, as alkaline, it was extracted twice with methylene chloride. Combined methylene chloride layer was washed with saturated aqueous sodium chloride solution, and thereafter was dried with anhydrous magnesium sulphate. The solvent was distilled off under reduced pressure, and an obtained oily substance was purified by column chromatography (20= 1 = eluate = chloroform = ethanol) using silica gel, and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline 410 mg was obtained as pale-brown oily substance.
NMR (400 MHz, CDCl3) δ ppm1.88-2.40 (6H, m), 3.69 (1H, quint), 6.71 (1H, ddd), 6.89 (1H, t), 6.93 (1H, s), 7.14 (1H, t).

(0093)

Reference Example 18

Ethyl 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzoic acid:

Ethyl 3-iodobenzoic acid 8.45 g, tetrakis (triphenyl phosphine) palladium (0) 1.77 g and 4-cyclobutyl-2-ethinyl thiazole 5 g were stirred under a stream of nitrogen at room temperature in diisopropylamine 100 ml for one hour. Oily substance obtained by distilling the reaction liquor under reduced pressure was purified by column chromatography (eluate = n-hexane : ethyl acetate = 8 : 1) using silica gel, and ethyl 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzoic acid 9.27 g were obtained as pale-brown oily substance.

IR ÉÀ max cm-12220.
NMR (400 MHz, CDCl3) δ ppm1.41 (3H, t), 1.91-2.42 (6H, m), 3.70 (1H, quint), 4.40 (2H, q), 6.97 (1H, s), 7.46 (1H, t), 7.75 (1H, dt), 8.06 (1H, dt), 8.28 (1H, t), MS(FAB)m/z 312 (M+ +1).

(0094)

Reference Example 19

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzoic acid:

Ethyl 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzoic acid 9.28 g were dissolved in THF100ml, and 0.25N sodium hydroxide aqueous solution 200 ml were added, and the mixture was stirred at room temperature for three hours. The reaction liquor was discharged in 1N hydrochloric acid 100 ml under ice cooled stirring. The precipitated crystals were recovered, and, after washing with water, it was air-dried. The obtained crude crystals were recrystallised from chloroform-n-hexane, and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzoic acid 6.85 g were obtained as straw-coloured minute needle crystal.

mp. 139-140°C.

IR v max cm-12220.

NMR (400 MHz, CDCl3) δ ppm1.90-2.45 (6H, m), 3.76 (1H, quint), 6.97 (1H, s), 7.50 (1H, t), 7.80 (1H, dt), 8.14 (1H, dt), 8.38 (1H, t), MS(FAB)m/z 284 (M+ +1).

Elemental analysis values C16H13NO2 S

Theoretical value (%) C, 67.82, H, 4.62, N, 4.94,

Measured value (%) C, 67.38, H, 4.63, N, 4.94..

(0095)

Reference Example 20

Ethyl 1-(4-methoxybenzyl)-tetrazole-5-carboxylate and ethyl 2-(4-methoxybenzyl)-tetrazole-5-carboxylate:

Trifluoroacetic acid 4 ml under ice cooled stirring was added to 2, 6-lutidine 22 ml. Cyano ethyl formate ester4.82g was added and sodium azide 3.25 g to the reaction liquor and was stirred at 70-80°C for five hours. After cooling, the reaction liquor was diluted with acetic acid ethyl ester 100 ml, and the precipitated crystals were recovered by filtration. This crystal was suspended in N,N-dimethylformamide 20 ml, and potassium carbonate 2.64 g and 4-methoxybenzyl chloride 6.19 g were added, and the mixture was stirred at 70-80°C for two hours. After cooling, water 100 ml were added to the reaction liquor, and extraction with toluene was carried out. The liquid extract was washed with water and thereafter, was dried with sodium sulfate. The residue obtained by elimination by distillation of the solvent was purified by column chromatography (eluate = n-hexane : ethyl acetate = 2 : 1) using silica gel, and ethyl 1 and 2-(4-methoxybenzyl)-tetrazole-5-carboxylate 11.7 g as a mixture of 1 position and 2-position in a 1 to 1 ratio was obtained as an oily substance. (both isomers can be separated with column chromatography using silica gel) NMR (400 MHz, CDCl3) δ ppm1.44 and 1.45 (3H, each t), 3.79 and 3.80 (3H, eachs), 4.51 and 4.52 (2H, each q), 5.78 and 5.86 (2H, each s), 6.86 and 6.89 (2H, each d), 7.35 and 7.38 (2H, each d).

(0096)

Reference Example 21

1-(4-methoxybenzyl)-tetrazole-5-carboxylic acid and 2-(4-methoxybenzyl)-tetrazole-5-carboxylic acid:

1N sodium hydroxide aqueous solution 3.5 ml and methanol 15 ml were added to mixture 0.77 g of ethyl 1-(4-methoxybenzyl)-tetrazole-5-carboxylate and ethyl 2-(4-methoxybenzyl)-tetrazole-5-carboxylate, and the mixture was stirred at room temperature for one hour. The reaction liquor was concentrated, and 1N hydrochloric acid 5 ml was added to the residue, and extraction was carried out with ethyl acetate. The liquid extract was washed with saturated aqueous sodium

chloride solution and thereafter, was dried with sodium sulfate. Ether-n-hexane was added to the residue obtained by the elimination of the solvent by distillation, and the precipitated crystals were recovered, and the title substance 0.45 of mixture of 2-position and 1 position in a 1: 1 ratio were obtained as prism crystals.

NMR (400 MHz, CDCl3) δ ppm3.80 and 3.82 (3H, each s), 5.53 and 5.79 (2H, eachs), 6.89 and 6.92 (2H, each d), 7.27 and 7.38 (2H, each d), 8.12 and 8.58 (1H, each s).

(0097)

Example 1

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole :

(Step 1). Synthesis of 3-iodobenzo nitrile

3-iodo benzamide 10.38 g were dissolved in 50ml of DMF, and 4.7ml of phosphorus oxychloride under stirring was added dropwise at 0°C. It was stirred at the same temperature for one hour, and thereafter the reaction liquor was poured into 500ml of iced water. The precipitated crystals were recovered by filtration, and it washed with water, and thereafter, it was dried, and 3-iodobenzo nitrile 9.23 g was obtained as prism crystals.

mp. 35-37°C.

NMR (400 MHz, CDCl3) δ ppm7.22 (1H, t), 7.64 (1H, dt), 7.95 (1H, dt), 7.99 (1H, t).

(0098)

Step 2

Synthesis of 3-(iodo phenyl)-1H-tetrazole

Sodium azide 33.35 g were suspended in DMF 150 ml, and aluminum chloride 15.20 g under stirring were gradually added at 0°C, and the mixture was stirred at room temperature for one hour. 8.70g3-iodo benzonitrile was added to the reaction liquor, and the mixture was stirred at 90°C for three hours. After cooling, the reaction liquor was stirred with ice-cooling, and thereafter discharged into 1N hydrochloric acid 300 ml. The precipitated crystals were recovered by filtration and, after washing with water, were dried. The crude crystals were recrystallised from chloroform-ethanol-n-hexane, and 3-(iodo phenyl)-1H-tetrazole 9.34 g was obtained as needle crystals.

mp. 170-172°C.

NMR (400 MHz, DMSO-d6) δ ppm7.42 (1H, dd), 7.96 (1H, d), 8.06 (1H, d), 8.39 (1H, s),

MS(FAB) m/z 273 (M+ +1).

Elemental analysis values 7C H5 IN4

Theoretical value (%) C, 30.90, H, 1.85, N, 21.59,

Measured value (%) C, 30.56, H, 1.89, N, 20.69..

(0099)

Step 3

Synthesis of 5-(3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole

3-(iodo phenyl)-1H-tetrazole 8.98 g and potassium carbonate 6.91 g were suspended in 50ml of DMF, and 4-methoxybenzyl chloride under ice cooled stirring was added dropwise. On completion of the dropwise addition, the reaction liquor was stirred at room temperature for 15 hours. Discharge was done of the reaction liquor to 300ml of water, and the precipitated crystals were recovered by filtration and, after washing with water, were dried. The obtained crude crystals were recrystallised from chloroform-n-hexane, and 5-(3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 11.43 g was obtained.

NMR (400 MHz, CDCl3) δ ppm3.80 (3H, s), 5.73 (2H, s), 6.90-6.92 (2H, m), 7.20 (1H, t), 7.37-7.39 (2H, m), 7.78 (1H, dt), 8.10 (1H, dt), 8.48 (1H, t), MS(FAB)m/z 393 (M+ +1).

Elemental analysis values C15H13IN4 O

Theoretical value (%) C, 45.94, H, 3.34, N, 14.29,

Measured value (%) C, 45.81, H, 3.35, N, 14.27..

(0100)

Step 4

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole

Diisopropylamine 100ml and DMF50ml was added to 5-(3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 23.53 g, tetrakis (triphenyl phosphine) (0) palladium 3.47 g and cuprous iodide 1.14 g and was under a stream of nitrogen stirred at room temperature for 0 hours 30 minutes. DMF solution 50 ml of 11.43g of 4-cyclobutyl-2-ethinyl thiazole were added dropwise to this reaction liquor and also were stirred at room temperature for two hours. The reaction liquor was diluted with 1000ml of ethyl acetate and was successively washed with 1N hydrochloric acid, saturated aqueous sodium chloride solution and thereafter was dried with sodium sulfate. the residue obtained by the elimination of the solvent by distillation was purified by column chromatography (eluate = ethyl acetate : n-hexane = 1 : 8) using silica gel, and it was crystallised from the n-hexane, and a thing of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 18.86 g was obtained as a crystalline powder.

mp. 87-89°C.

NMR (400 MHz, CDCl3) δ ppm1.90-2.42 (6H, m), 3.66-3.75 (1H, m), 3.80 (3H, s), 5.74 (2H, s), 6.90-6.92 (2H, m), 6.97 (1H, s), 7.39-7.41 (2H, m), 7.48 (1H, t), 7.65 (1H, d), 8.16 (1H, d), 8.37 (1H, s), MS(EI)m/z 427(M+).

Elemental analysis values C24H21N5 OS

Theoretical value (%) C, 67.43, H, 4.95,N, 16.38,

Measured value (%) C, 67.21, H, 5.02, N, 16.27..

(0101)

Step 5

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 17.96 g was dissolved in anisole 8 ml and trifluoroacetic acid 40 ml and was stirred at room temperature for 14 hours and at 60 °C for two hours. The reaction liquor was poured into 500ml of iced water, and the precipitated crystals were recovered by filtration and were dried after having washed with water. The obtained crude crystals were recrystallised from chloroform-ethanol-n-hexane, and 11.01 g title substance was obtained as a crystalline powder.

mp. 190-193°C.

IR ÉÀ max cm-12220.

NMR (400 MHz, DMSO-d6) δ ppm1.84-2.35 (6H, m), 3.64-3.73 (1H, m), 7.57 (1H, s), 7.73 (1H, t), 7.88 (1H, d), 8.16 (1H, d), 8.29 (1H, s), MS(EI)m/z 307(M+).

Elemental analysis values C16H13N5 S

Theoretical value (%) C, 62.52, H, 4.26, N, 22.78,

Measured value (%) C, 62.33, H, 4.35, N, 22.62..

(0102)

Example 2

5-(3-(2-(2-thiazolyl) ethinyl) phenyl)-1H-tetrazole :

Step 1

Synthesis of methyl 3-(1H-tetrazol-5-yl) phenylacetate.

Methyl 3-cyanophenyl acetate 3.10 g were treated in the same way as in Step 2 of Example 1, and the obtained crude crystals were recrystallised from ethanol-n-hexane, and methyl 3-(1H-tetrazol-5-yl) phenylacetate 1.72 g were obtained as needle crystals.

mp. 141-142°C.

IR ÉÀ max cm-11732.

NMR (400 MHz, DMSO-d6) δ ppm3.68 (3H, s), 3.77 (2H, s), 7.44-7.55 (2H, m), 7.95-8.00 (2H, m).

Elemental analysis values C10H10N4 O2

Theoretical value (%) C, 55.04, H, 4.62, N, 25.68,

Measured value (%) C, 55.08, H, 4.64, N, 25.78..

(0103)

Step 2

Synthesis of methyl 3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) phenylacetate

Methyl 3-(1H-tetrazol-5-yl) phenylacetate 1.67 g were treated in the same way as in Step 3 of Example 1, and methyl 3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) phenylacetate 2.06 g were obtained as an oily substance.

NMR (400 MHz, CDCl3) δ ppm3.70 (3H, s), 3.75 (2H, s), 3.79 (3H, s), 5.73 (2H, s), 6.89 (2H, d), 7.38 (2H, d), 7.40-7.45 (3H, m), 8.05 (1H, d).

(0104)

Step 3

Synthesis of 2-(4-methoxybenzyl)-5-(3-(2-oxo-2-(2-thiazolyl) ethyl)-2H-tetrazole

2-bromothiazole 2.25 g was dissolved in THF30ml, and magnesium bromide bromide (THF solution of 0.95M) 15 ml were added while stirring with ice-cooling. It was stirred at room temperature for one hour, and thereafter, THF10ml solution of 3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) phenylacetate 2.00 g cooled to 0°C again was added dropwise. It was stirred at room temperature for one hour, and thereafter, 1N hydrochloric acid was added, and extraction was carried out with ethyl acetate. the liquid extract was washed with water and saturated aqueous sodium chloride solution and thereafter was dried with sodium sulfate. The residue obtained by elimination by distillation of the solvent was purified by column chromatography (eluate = ethyl acetate : n-hexane = 1 : 4) using silica gel, and obtained crystal was recrystallised from ether-n-hexane, and 2-(4-methoxybenzyl)-5-(3-(2-oxo-2-(2-thiazolyl) ethyl)-2H-tetrazole 1.81 g was obtained as needle crystals.

mp. 80-81°C.

IR ÉÀ max cm-11678.

NMR (400 MHz, CDCl3) δ ppm3.80 (3H, s), 4.54 (2H, s), 6.89 (2H, d), 7.38 (2H, d), 7.39-7.46 (2H, m), 7.70 (1H, d), 8.04 (1H, d).

Elemental analysis values C20H17N5 O2 S

Theoretical value (%) C, 61.37, H, 4.38,N, 17.89,

Measured value (%) C, 61.11, H, 4.51, N, 17.82..

(0105)

Step 4

Synthesis of 2-(4-methoxybenzyl) 5-(3-(2-(2-thiazolyl) ethinyl) phenyl)-2H-tetrazole

1, 2-chloroethane 15 ml were added to triphenyl phosphine oxide 1.56 g, and trifluoromethane sulfonic acid anhydride 0.80 g was added with stirring with ice cooling and was stirred at the same temperature for 15 minutes. To the reaction liquor, triethylamine 1.2 ml and 2-(4-methoxybenzyl)-5-(3-(2-oxo-2-(2-thiazolyl) ethyl)-2H-tetrazole 0.73 g were added, and the mixture was heated under reflux for 20 hours. After cooling, the reaction liquor was diluted with

chloroform 50 ml and was successively washed with 1N hydrochloric acid, water and thereafter, was dried with sodium sulfate. The residue obtained by elimination by distillation of the solvent was purified by column chromatography (eluate = ethyl acetate : n-hexane = 1 : 3) using silica gel, and the obtained crystals were recrystallised from chloroform-ether, and 2-(4-methoxybenzyl)-5-(3-(2-(2-thiazolyl) ethinyl) phenyl)-2H-tetrazole 0.21 g was obtained as needle crystals.
mp. 95-96°C.
IR ÉÀ max cm-12216.
NMR (400 MHz, CDCl3) δ ppm3.80 (3H, s), 5.73 (2H, s), 6.91 (2H, d), 7.36-7.43 (3H, m), 7.49 (1H, t), 7.67 (1H, ddd), 7.88 (1H, d), 8.18 (1H, ddd), 8.37 (1H, dd).
Elemental analysis values C20H15N5 OS
Theoretical value (%) C, 64.33, H, 4.05, N, 4.05,
Measured value (%) C, 64.23, H, 4.19, N, 18.79..

(0106)

Step 5

Synthesis of 5-(3-(2-(2-thiazolyl) ethinyl) phenyl)-1H-tetrazole

2-(4-methoxybenzyl)-5-(3-(2-(2-thiazolyl) ethinyl) phenyl)-2H-tetrazole 150 mg was treated in the same way as in Step 5 of Example 1, and the obtained crude crystals were recrystallised from ethanol-ether, and the title substance 30 mg was obtained as a crystalline powder.
mp. 174-175°C.
IR ÉÀ max cm-12216.
NMR (400 MHz, DMSO-d6) δ ppm7.75 (1H, s), 7.88 (1H, d), 7.99 (1H, d), 8.02 (1H, d), 8.17 (1H, d), 8.39 (1H, s).
Elemental analysis values C12H7 N5 S
Theoretical value (%) C, 56.90, H, 2.79, N, 27.65,
Measured value (%) C, 57.14, H, 2.87, N, 26.84..

(0107)

Example 3

5-(3-(2-(2-benzothiazolyl) ethinyl) phenyl)-1H-tetrazole :

Step 1

Synthesis of 2-(2-(3-(2-[4-methoxybenzyl]-2H-tetrazol-5-yl) phenyl) ethinyl) benzothial.

2-ethinyl benzothiazole 318 mg and 5-(3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 784 mg were subjected to coupling reaction same as in Step 4 of Example 1, and it was crystallised from the n-hexane, and 2-(2-(3-(2-[4-methoxybenzyl]-2H-tetrazol-5-yl) phenyl) ethinyl) benzothiazole 468 mg was obtained as pale-brown crystalline powder.
mp. 133-135°C.

NMR (400 MHz, CDCl3) δ ppm3.80 (3H, s), 5.75 (2H, s), 6.90-6.93 (2H, m), 7.39-7.43 (2H, m), 7.47 (1H, t), 7.50-7.56 (2H, m), 7.71 (1H, d), 7.89 (1H, d), 8.09 (1H, d), 8.20 (1H, d), 8.42 (1H, s).

(0108)

Step 2

Synthesis of 5-(3-(2-(2-benzothiazolyl) ethinyl) phenyl)-1H-tetrazole

De-4-methoxybenzylation reaction was carried out in the same way as in Step 5 of Example 1 by 2-(2-(3-(2-[4-methoxybenzyl]-2H-tetrazol-5-yl) phenyl) ethinyl) benzothiazole 423 mg, and crude crystals were recrystallised from chloroform-ethanol, and the title substance was obtained.

mp. 208-210°C.

NMR (400 MHz, DMSO-d6) δ ppm7.56-7.65 (2H, m), 7.75 (1H, t), 7.94 (1H, d), 8.11 (1H, d), 8.19-8.21 (2H, m), 8.36 (1H, s), MS(FAB)m/z 304 (M+ +1).

Elemental analysis values C16H9 N5 S/1 /4 H2 O

Theoretical value (%) C, 62.43, H, 3.11, N, 22.75,

Measured value (%) C, 62.60,H, 3.00, N, 22.56..

(0109)

Example 4

5-(3-(2-(4-n-propyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole :

Step 1

Synthesis of 5-(3-(2-(4-n-propyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

4-n-propyl-2-ethinyl thiazole and 5-(3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole were used, and it was treated in the same way as in Step 5 of Example 1, and 5-(3-(2-(4-n-propyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as pale yellow acicular crystals.

mp. 57-58°C.

NMR (400 MHz, CDCl3) δ ppm0.98 (3H, t), 1.77 (2H, m), 2.79 (2H, t), 3.84 (3H, s), 5.74 (2H, s), 6.91 (2H, d), 6.96 (1H, s), 7.41 (2H, d), 7.48 (1H, t), 7.65 (1H, dt), 8.16 (1H, dt), 8.36 (1H, t).

Elemental analysis values C23H21N5 OS/1 /4 H2 O

Theoretical value (%) C, 65.77, H, 5.16, N, 16.67,

Measured value (%) C, C, 66.21, H, 5.15, N, 16.30..

(0110)

Step 2

Synthesis of 5-(3-(2-(4-n-propyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole

5-(3-(2-(4-n-propyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated same as Step 5 of Example 1, and the obtained crude crystals were recrystallised from water-ethanol, and the title substance was obtained as a crystalline powder.

mp. 154-156°C.

NMR (400 MHz, DMSO-d6) δ ppm0.93 (3H, t), 1.70 (2H, m), 2.74 (2H, t), 7.52 (1H, s), 7.71 (1H, t), 7.84 (1H, d), 8.16 (1H, d), 8.28 (1H, s).

Elemental analysis values C15H13N5 S

Theoretical value (%) C, 61.00, H, 4.44, N, 23.71,

Measured value (%) C, 61.01, H, 4.48, N, 23.55..

(0111)

Example 5

5-(3-(2-(4-cyclopropyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole :

Step 1

Synthesis of 5-(3-(2-(4-cyclopropyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

4-cyclopropyl-2-ethinyl thiazole 1.04 g and 5-(3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 2.73 g were treated in the same way as in Step 5 of Example 1, and 2.13g of 5-(3-(2-(4-cyclopropyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as needle crystals.

mp. 106-107°C.

NMR (400 MHz, CDCl3) δ ppm0.94-0.99 (4H, m), 2.04-2.11 (1H, m), 3.80 (3H, s), 5.74 (2H, s), 6.91 (1H, s), 6.89-6.93 (2H, m), 7.40 (2H, d), 7.47 (1H, t), 7.65 (1H, dd), 8.15 (1H, dd), 3.35 (1H, t), MS(FAB)m/z 414(M+).

(0112)

Step 2

Synthesis of 5-(3-(2-(4-cyclopropyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole

5-(3-(2-(4-cyclopropyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 2.07 g was treated in the same way as in Step 5 of Example 1, and the obtained crude crystals were recrystallised from chloroform-n-hexane, and the title substance 1.16 g was obtained as needle crystals.

mp. 184-185°C (decomp.).

IR ÉÀ max cm-12216, NMR (400 MHz, DMSO-d6) δ ppm0.84-0.90 (2H, m), 0.92-0.98 (1H, m), 2.09-2.19 (1H, m), 7.54 (1H, s), 7.72 (1H, t), 7.86 (1H, d), 8.16 (1H, d), 8.28 (1H, s), MS(FAB)m/z 294 (M+ +1).

Elemental analysis values C15H11N5 S/1 /2 H2 O

Theoretical value (%) C, 59.59, H, 4.00, N, 23.16,
Measured value (%) C, 59.75, H, 3.80, N, 23.02..

(0113)

Example 6

5-(3-(2-(4-isopropyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole :.

Step 1.

Synthesis of 5-(3-(2-(4-isopropyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole

4-isopropyl-2-ethinyl thiazole 850 mg and 5-(3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 2.55 g were treated in the same way as in Step 5 of Example 1, and it was purified by column chromatography (eluate = ethyl acetate : n-hexane = 1 : 8) using silica gel, and 5-(3-(2-(4-isopropyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 1.08 g was obtained as pale-brown oily substance.

NMR (400 MHz, CDCl3) δ ppm1.35 (6H, d), 3.16 (1H, m), 3.81 (3H, s), 5.74 (2H, s), 6.91 (2H, dt), 6.96 (1H, d), 7.41 (2H, dt), 7.48 (1H, t), 7.66 (1H, dt), 8.16 (1H, dt), 8.37 (1H, t).

(0114)

Step 2

Synthesis of 5-(3-(2-(4-isopropyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole

5-(3-(2-(4-isopropyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 1.85 g was treated in the same way as in Step 5 of Example 1, and the obtained crude crystals were recrystallised from chloroform-iso pro pili ether, and the title substance 383 mg was obtained as pale-brown crystalline powder.

mp. 177-179°C.

NMR (400 MHz, DMSO-d6) δ ppm1.44 (6H, d), 3.25 (1H, m), 7.70 (1H, s), 7.88 (1H, t), 8.03 (1H, d), 8.32 (1H, d), 8.45 (1H, s).

Elemental analysis values C15H13N5 S
Theoretical value (%) C, 61.00, H, 4.44, N, 23.71,
Measured value (%) C, 61.05, H, 4.54, N, 23.88..

(0115)

Example 7

5-(3-(2-(4-tert-butyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole :

Step 1.

Synthesis of 5-(3-(2-(4-tert-butyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole

4-tert-butyl-2-ethinyl thiazole 402 mg and 5-(3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 2.73 g were treated in the same way as in Step 5 of Example 1, and it was purified by column

chromatography (eluate = ethyl acetate : n-hexane = 1 : 10) using silica gel, and it was crystallised from the n-hexane, and 5-(3-(2-(4-tert-butyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 1.91 g was obtained.
mp. 113-115°C.
NMR (400 MHz, CDCl3) δ ppm1.39 (9H, s), 3.80 (3H, s), 5.74 (2H, s), 6.91 (2H, d), 6.98 (1H, s), 7.40 (2H, d), 7.48 (1H, t), 7.66 (1H, dt), 8.16 (1H, dt), 8.37 (1H, t), MS(FAB)m/z 430 (M+ +1).

(0116)

Step 2

Synthesis of 5-(3-(2-(4-tert-butyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole

5-(3-(2-(4-tert-butyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 1.73 g was treated in the same way as in Step 5 of Example 1, and the obtained crude crystals were recrystallised from chloroform-IPE, and the title substance 1.06 g was obtained as needle crystals.
mp. 176-178°C.
NMR (400 MHz, DMSO-d6) δ ppm1.33 (9H, s), 7.54 (1H, s), 7.73 (1H, t), 7.88 (1H, d), 8.17 (1H, d), 8.30 (1H, s), MS(FAB)m/z 310 (M+ +1).
Elemental analysis values C16H15N5 S/1 /5 H2 O
Theoretical value (%) C, 61.22, H, 4.98,N, 22.31,
Measured value (%) C, 61.27, H, 4.87, N, 22.14..

(0117)

Example 8

5-(3-(2-(4-isopropyl-5-methyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole =. Step 1. Synthesis of 5-(3-(2-(4-isopropyl-5-methyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole
4-isopropyl-5-methyl-2-ethinyl thiazole 240 mg and 5-(3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 471 mg were treated in the same way as in Step 5 of Example 1, and it was purified by column chromatography (eluate = ethyl acetate : n-hexane = 1 : 8) using silica gel, and it was crystallised from the n-hexane, and 5-(3-(2-(4-isopropyl-5-methyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 1.91 g was obtained as needle crystals.
mp. 101-103°C.
NMR (400 MHz, CDCl3) δ ppm1.31 (6H, d), 2.41 (3H, s), 3.09 (1H, m), 3.80 (3H, s), 5.74 (2H, s), 6.91 (2H, d), 7.40 (2H, d), 7.46 (1H, br t), 7.64 (1H, d), 8.14 (1H, d), 8.35 (1H, s).

(0118)

Step 2

Synthesis of 5-(3-(2-(4-isopropyl-5-methyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole

5-(3-(2-(4-isopropyl-5-methyl 2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 387 mg was treated in the same way as in Step 5 of Example 1, and the obtained crude crystals were recrystallised from chloroform-n-hexane, and the title substance 206 mg was obtained as a crystalline powder.

mp. 153-155°C.

NMR (400 MHz, DMSO-d6) δ ppm1.22 (6H, d), 2.43 (3H, s), 3.14 (1H, m), 7.71 (1H, br t), 7.86 (1H, d), 8.15 (1H, d), 8.27 (1H, s), MS(FAB)m/z 310 (M+ +1).

Elemental analysis values C16H15N5 S

Theoretical value (%) C, 62.11,H, 4.89, N, 22.64,

Measured value (%) C, 61.99, H, 4.92, N, 22.86..

(0119)

Example 9

5-(3-(2-(4-cyclopentyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole =. Step 1. Synthesis of 5-(3-(2-(4-cyclopentyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole

4-cyclopentyl-2-ethinyl thiazole 249 mg and 5-(3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 500 mg were treated in the same way as in Step 5 of Example 1, and it was purified by column chromatography (eluate = ethyl acetate : n-hexane = 1 : 8) using silica gel, and 5-(3-(2-(4-cyclopentyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 420 mg was obtained as pale-brown oily substance.

NMR (400 MHz, CDCl3) δ ppm1.65-2.85 (8H, m), 3.24 (1H, m), 3.80 (3H, s), 5.74 (2H, s), 6.91 (2H, d), 6.96 (1H, s), 7.40 (2H, d), 7.48 (1H, t), 7.64 (1H, dt), 8.15 (1H, dt), 8.37 (1H, t).

(0120)

Step 2

Synthesis of 5-(3-(2-(4-cyclopentyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole

5-(3-(2-(4-cyclopentyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 400 mg was treated in the same way as in Step 5 of Example 1, and the obtained crude crystals were recrystallised from chloroform-ethanol-n-hexane, and the title substance 280 mg was obtained as fine needle crystal.

mp. 145°C (decomp.).

NMR (400 MHz, CDCl3-DMSO-d6) δ ppm1.60-2.75 (8H, m), 3.25 (1H, m), 7.00 (1H, s), 7.54 (1H, t), 7.71 (1H, d), 8.17 (1H, d), 8.37 (1H, s), MS(EI)m/z 321(M+).

(0121)

Example 10

5-(3-(2-(4-cyclohexyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole :

Step 1.

Synthesis of 5-(3-(2-(4-cyclohexyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole

4-cyclohexyl-2-ethinyl thiazole 268 mg and 5-(3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 500 mg were treated in the same way as in Step 5 of Example 1, and it was purified by column chromatography (eluate = ethyl acetate : n-hexane = 1 : 8) using silica gel, and 5-(3-(2-(4-cyclohexyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 400 mg was obtained as pale-brown oily substance.

NMR (400 MHz, CDCl3) δ ppm1.25-2.15 (10H, m), 2.81 (1H, m), 3.81 (1H, s), 5.74 (2H, s), 6.92 (2H, d), 6.93 (1H, s), 7.41 (2H, d), 7.65 (1H, dt), 8.15 (1H, dt), 8.36 (1H, t).

(0122)

Step 2

Synthesis of 5-(3-(2-(4-cyclohexyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole

5-(3-(2-(4-cyclohexyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 473 mg was treated in the same way as in Step 5 of Example 1, and the obtained crude crystals were recrystallised from chloroform-ethanol-n-hexane, and the title substance 240 mg was obtained as fine needle crystal.

mp. 166-169°C.

IR ÉÀ max cm-12216.

NMR (400 MHz, CDCl3) δ ppm1.25-2.20 (10H, m), 2.96 (1H, m), 7.05 (1H, s), 7.55 (1H, dd), 8.15 (1H, s), 8.16 (1H, dd), MS(EI)m/z 335(M+).

Elemental analysis values C18H17N5 S

Theoretical value (%) C, 64.45, H, 5.11, N, 20.88,

Measured value (%) C, 64.46,H, 5.10, N, 20.62..

(0123)

Example 11

5-(3-(2-(4-methylthiomethyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole =. Step 1. Synthesis of 2-(4-methoxybenzyl)-5-(3-(2-(4-methylthiomethyl-2-thiazolyl) ethinyl) phenyl)-2H-tetrazole

2-ethinyl-4-methylthio thiazole 508 mg and 5-(3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 981 mg were subjected to coupling reaction same as in Step 4 of Example 1, and it was purified by column chromatography (eluate = ethyl acetate : n-hexane = 1 : 4) using silica gel, and it was recrystallised from chloroform-n-hexane, and 2-(4-methoxybenzyl)-5-(3-(2-(4-methylthiomethyl-2-thiazolyl) ethinyl) phenyl)-2H-tetrazole 867 mg was obtained as straw-coloured crystalline powder.

mp. 104-106°C.

NMR (400 MHz, CDCl3) δ ppm2.14 (3H, s), 3.81 (3H, s), 3.86 (2H, s), 5.74 (2H, s), 6.90-6.93 (2H, m), 7.21 (1H, s), 7.39-7.41 (2H, m), 7.49 (1H, t), 7.65 (1H, d), 8.17 (1H, d), 8.36 (1H, s), MS(EI)m/z 433(M+).

Elemental analysis values C22H19N5 S2

Theoretical value (%) C, 60.95, H, 4.42, N, 16.15,

Measured value (%) C, 60.66, H, 4.45, N, 16.10..

(0124)

Step 2

Synthesis of 5-(3-(2-(4-methylthiomethyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole

2-(4-methoxybenzyl)-5-(3-(2-(4-methylthiomethyl-2-thiazolyl) ethinyl) phenyl)-2H-tetrazole 433 mg was treated with Step 5 of Example 1, and crude crystals were recrystallised from chloroform-n-hexane, and the title substance 285 mg was obtained.

mp. 159-162°C.

NMR (400 MHz, DMSO-d6) δ ppm2.07 (3H, s), 3.85 (2H, s), 7.71 (1H, s), 7.73 (1H, t), 7.88 (1H, dt), 8.17 (1H, dt), 8.29 (1H, t), MS(EI)m/z 313(M+).

Elemental analysis values C14H11N5 S2/1 /4 H2 O

Theoretical value (%) C, 52.89, H, 3.65, N, 22.03,

Measured value (%) C, 52.87, H, 3.54, N, 21.70..

(0125)

Example 12

5-(3-(2-(4-methoxymethyl-5-methyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole =. Step 1.

Synthesis of 2-(4-methoxybenzyl)-5-(3-(2-(4-methoxymethyl-2-thiazolyl) ethinyl) phenyl)-2H-tetrazole

2-ethinyl-4-methoxymethyl thiazole 659 mg and 5-(3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 1.41 g were treated in the same way as in Step 4 of Example 1, and product was purified by column chromatography (eluate = ethyl acetate : n-hexane-chloroform = 2 : 1) using silica gel, and it was recrystallised from chloroform-n-hexane, and 2-(4-methoxybenzyl)-5-(3-(2-(4-methoxymethyl-2-thiazolyl) ethinyl) phenyl)-2H-tetrazole 1.487 g was obtained as a crystalline powder.

mp. 105-107°C.

NMR (400 MHz, CDCl3) δ ppm3.49 (3H, s), 3.80 (3H, s), 4.63 (2H, s), 5.74 (2H, s), 6.90-6.92 (2H, m), 7.30 (1H, s), 7.39-7.41 (2H, m), 7.49 (1H, t), 7.65 (1H, d), 8.17 (1H, d), 8.36 (1H, s), MS(EI)m/z 417(M+).

Elemental analysis values C22H19N5 O2 S

Theoretical value (%) C, 63.29, H, 4.59, N, 16.77,

Measured value (%) C, 63.12, H, 4.62, N, 16.66..

(0126)

Step 2

Synthesis of 5-(3-(2-(4-methoxymethyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole

2-(4-methoxybenzyl)-5-(3-(2-(4-methoxymethyl-2-thiazolyl) ethinyl) phenyl)-2H-tetrazole 1.169 g was treated in the same way as in Step 5 of Example 1, and crude crystals were recrystallised from ethanol-n-hexane, and the title substance 794 mg was obtained.

mp. 211-214°C.

IR ÉÀ max cm-12216.

NMR (400 MHz, DMSO-d6) δ ppm3.35 (3H, s), 4.54 (2H, s), 7.73 (1H, s), 7.80 (1H, t), 7.87 (1H, dt), 8.17 (1H, dt), 8.29 (1H, t), MS(EI)m/z 297(M+), elemental analysis values C14H11N5 OS

Theoretical value (%) C, 56.55, H, 3.73, N, 23.55,

Measured value (%) C, 56.52, H, 3.84, N, 23.66..

(0127)

Example 13

5-(3-(2-(4-methyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole :

Step 1

Synthesis of 5-(3-(2-(4-methyl-2-thiazolyl)-2-oxoethyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

Diisopropylamine 1.04 g were dissolved in THF20ml, and n-butyllithium (n-hexane solution of 1.71M) 5.6 ml under stirring were added at-78°C, and the mixture was stirred at 0°C for ten minutes. It was cooled again to 78°C and THF5ml solution of 4-methylthiazol 1.00 g was added and the mixture was stirred at the same temperature for 0 hours 30 minutes. THF solution of methyl 3-(2-(4-methoxybenzyl)-5-tetrazolyl) phenylacetic acid 1.45 g was added to the reaction liquor and also was stirred at the same temperature for one hour. Water was added to the reaction liquor, and it was returneed to room temperature, and was acidified by adding 1N hydrochloric acid, and thereafter extraction was carried out with ethyl acetate. Water and saturated aqueous sodium chloride solution were used to successively wash the liquid extract and thereafter, the extract were dried with sodium sulfate. the solvent was eliminated by distillation, and the residue was purified by column chromatography (eluate = ethyl acetate : n-hexane = 1 : 3) using silica gel, and it was recrystallised, and 5-(3-(2-(4-methyl-2-thiazolyl)-2-oxoethyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 0.60 g was obtained as needle crystal from ether-n-hexane.

mp. 90-91°C.

NMR (400 MHz, CDCl3) δ ppm2.52 (3H, s), 3.79 (3H, s), 4.51 (2H, s), 5.72 (2H, s), 6.89 (2H, d), 7.37 (2H, d), 7.40-7.45 (3H, m), 8.04 (1H, t), 8.12 (1H, s).

Elemental analysis values C21H19N5 O2 S
Theoretical value (%) C, 62.11, H, 4.92, N, 17.27,
Measured value (%) C, 61.78, H, 4.78, N, 16.99..

(0128)

Step 2

Synthesis of 5-(3-(2-(4-methyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole

5-(3-(2-(4-methyl-2-thiazolyl)-2-oxoethyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 3 of Example 2, and product was purified by column chromatography (eluate = ethyl acetate : n-hexane = 1 : 3) using silica gel, and obtained crystal was recrystallised from ether-n-hexane, and 5-(3-(2-(4-methyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 29 mg was obtained as needle crystals.
mp. 95-96°C.
NMR (400 MHz, CDCl3) δ ppm2.50 (3H, s), 3.80 (3H, s), 5.74 (2H, s), 6.91 (2H, d), 6.95 (1H, s), 7.40 (2H, d), 7.48 (1H, t), 7.64 (1H, d), 8.16 (1H, d), 8.36 (1H, s).

(0129)

Step 3

Synthesis of 5-(3-(2-(4-methyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole

5-(3-(2-(4-methyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 12.1 mg was treated in the same way as in Step 5 of Example 1, and crude crystals were recrystallised from ethanol-ether, and the title substance 6 mg was obtained.
mp. 224-227°C (decomp.).
NMR (400 MHz, DMSO-d6) δ ppm2.43 (3H, s), 7.53 (1H, s), 7.72 (1H, t), 7.85 (1H, d), 8.17 (1H, d), 8.27 (1H, s), MS(EI)m/z 267(M+).
Elemental analysis values C13H9 N5 S/1 /10 H2 O
Theoretical value (%) C, 58.02, H, 3.45, N, 26.02,
Measured value (%) C, 58.06, H, 3.69, N, 25.49..

(0130)

Example 14

5-(3-(2-(4-isobutyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole =. Step 1. Synthesis of 5-(3-(2-(4-isobutyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole

2-ethinyl-4-isobutyl thiazole 480 mg and 5-(3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 880 mg were treated in the same way as in Step 4 of Example 1, and product was purified by column chromatography (eluate = ethyl acetate : n-hexane = 1 : 4) using silica gel, and it was

recrystallised from chloroform-n-hexane, and 5-(3-(2-(4-isobutyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 867 mg was obtained as pale-brown oily substance.
NMR (400 MHz, CDCl3) δ ppm0.95 (6H, d), 2.12 (1H, m), 2.67 (2H, d), 3.80 (3H, s), 5.74 (2H, s), 6.91 (2H, d), 6.94 (1H, s), 7.40 (2H, d), 7.48 (1H, t), 7.64 (1H, d), 8.15 (1H, d), 8.36 (1H, s).

(0131)

Step 2

Synthesis of 5-(3-(2-(4-isobutyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole

5-(3-(2-(4-isobutyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 970 mg was treated in the same way as in Step 5 of Example 1, and crude crystals were recrystallised from chloroform-n-hexane, and the title substance 360 mg was obtained.
mp. 177-178°C.
NMR (400 MHz, DMSO-d6) δ ppm0.90 (6H, d), 2.03 (1H, m), 2.63 (2H, d), 7.54 (1H, s), 7.73 (1H, t), 7.86 (1H, d), 8.16 (1H, d), 8.32 (1H, s), MS(EI)m/z 309(M+).
Elemental analysis values C16H15N5 S/1 /4 H2 O
Theoretical value (%) C, 61.22, H, 4.98, N, 22.31,
Measured value (%) C, 60.90, H, 4.86, N, 21.97..

(0132)

Example 15

5-(3-(2-(4-ethyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole =. Step 1. Synthesis of 5-(3-(2-(4-ethyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole

4-ethyl-2-ethinyl-thiazole 460 mg and 5-(3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 1.0 g were treated in the same way as in Step 4 of Example 1, and product was purified by column chromatography (eluate = ethyl acetate : n-hexane = 1 : 3) using silica gel, and it was recrystallised from ethanol-n-hexane, and 5-(3-(2-(4-ethyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 730 mg was obtained as pale yellow needle crystal.
mp. 116-117°C.
NMR (400 MHz, CDCl3) δ ppm1.34 (3H, t), 2.85 (2H, q), 3.80 (3H, s), 6.90 (2H, d), 6.96 (1H, s), 7.39 (2H, d), 7.48 (1H, t), 7.66 (1H, d), 8.15 (1H, d), 8.36 (1H, s).
Elemental analysis values C22H19N5 OS/1 /2 H2 O
Theoretical value (%) C, 64.37, H, 4.91, N, 17.06,
Measured value (%) C, 64.62, H, 4.78, N, 16.73..

(0133)

Step 2

Synthesis of 5-(3-(2-(4-ethyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole

5-(3-(2-(4-ethyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 736 mg was treated in the same way as in Step 5 of Example 1, and crude crystals were recrystallised from ethanol-ether, and the title substance 268 mg was obtained as straw-coloured crystalline powder.
mp. 198-200°C.
NMR (400 MHz, DMSO-d6) δ ppm1.26 (3H, t), 2.78 (2H, q), 7.54 (1H, s), 7.73 (1H, t), 7.86 (1H, d), 8.16 (1H, d), 8.29 (1H, s), elemental analysis values C14H11N5 S
Theoretical value (%) C, 59.77, H, 3.94, N, 24.89,
Measured value (%) C, 59.30, H, 4.07, N, 24.71..

(0134)

Example 16

5-(3-(2-(4-n-octyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole =. Step 1. Synthesis of 2-(4-methoxybenzyl)-5-(3-(2-(4-n-octyl-2-thiazolyl) ethinyl) phenyl)-2H-tetrazole
2-ethinyl-4-n-octyl thiazole 410 mg and 5-(3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 726 mg were treated in the same way as in Step 4 of Example 1, and product was purified by column chromatography (eluate = ethyl acetate : n-hexane = 1 : 7) using silica gel and was crystallised from the n-hexane, and 2-(4-methoxybenzyl)-5-(3-(2-(4-n-octyl-2-thiazolyl) ethinyl) phenyl)-2H-tetrazole 593 mg was obtained as straw-coloured crystalline powder.
mp. 47-48°C.
NMR (400 MHz, CDCl3) δ ppm0.88 (3H, t), 1.27-1.75 (12H, m), 2.80 (2H, t), 3.79 (3H, s), 5.55 (2H, s), 6.89-6.92 (2H, m), 6.94 (1H, s), 7.38-7.41 (2H, m), 7.47 (1H, t), 7.64 (1H, d), 8.15 (1H, d), 8.36 (1H, s), MS(EI)m/z 485(M+).
Elemental analysis values C28H31N5 OS
Theoretical value (%) C, 69.24,H, 6.43, N, 14.42,
Measured value (%) C, 68.98, H, 6.32, N, 14.35..

(0135)

Step 2

Synthesis of 5-(3-(2-(4-n-octyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole
2-(4-methoxybenzyl)-5-(3-(2-(4-n-octyl-2-thiazolyl) ethinyl) phenyl)-2H-tetrazole 486 mg was treated in the same way as in Step 5 of Example 1, and crude crystals were recrystallised from chloroform-n-hexane, and the title substance 186 mg was obtained as a crystalline powder.
mp. 104-105°C.
NMR (400 MHz, DMSO-d6) δ ppm0.86 (3H, t), 1.25-1.68 (12H, m), 2.74 (2H, t), 7.53 (1H, s), 7.72 (1H, t), 7.86 (1H, d), 8.16 (1H, d), 8.28 (1H, s), MS(EI)m/z 365(M+).
Elemental analysis values C20H23N5 S
Theoretical value (%) C, 65.72, H, 6.34, N, 19.17,

Measured value (%) C, 65.69, H, 6.27, N, 19.24..

(0136)

Example 17

5-(4-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-thienyl)-1H-tetrazole :

Step 1

Synthesis of 5-(4-bromo-2-thienyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(4-bromo-2-thienyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(4-bromo-2-thienyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 70-72°C (recrystallization solvent = chloroform-n-hexane).

IR ÉÀ max cm-1,3108, 3004, 2964, 2836, 1682, 1614, 1588, 1574, 1516.

NMR (400 MHz, CDCl3) δ ppm3.80 (3H, s), 5.70 (2H, s), 6.88-6.91 (2H, m), 7.31 (1H, d), 7.35-7.38 (2H, m), 7.67 (1H, d), MS(EI)m/z 352 350((M+) +1).

Elemental analysis values C13H11BrN4 OS

Theoretical value (%) C, 44.46, H, 3.16, N, 15.95,

Measured value (%) C, 44.54, H, 3.11, N, 15.99..

(0137)

Step 2

Synthesis of 5-(4-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-thienyl)-1H-tetrazole

5-(4-bromo-2-thienyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and continuing, de-4-methoxybenzylation reaction was carried out in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 224-230°C (recrystallization solvent = chloroform-n-hexane).

IR ÉÀ max cm-1,3088, 2216, 1580, 1518.

NMR (400 MHz, DMSO-d6) δ ppm1.84-2.31 (6H, m), 3.63-3.71 (1H, m), 7.54 (1H, s), 7.93 (1H, s), 8.40 (1H, s), MS(FAB)m/z 314 (M+ +1).

Elemental analysis values C14H11N5 S2

Theoretical value (%) C, 52.15,H, 3.75, N, 21.72,

Measured value (%) C, 52.15, H, 3.67, N, 21.91..

(0138)

Example 18

5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-thienyl)-1H-tetrazole :

Step 1

Synthesis of 5-(5-bromo-2-thienyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(5-bromo-2-thienyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(5-bromo-2-thienyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.
mp. 87-89°C (recrystallization solvent = chloroform-n-hexane).
IR ÉÀ max cm-1,3000, 2840, 1614, 1580, 1520.
NMR (400 MHz, CDCl3) δ ppm3.79 (3H, s), 5.69 (2H, s), 6.88-6.91 (2H, m), 7.07 (1H, d), 7.37-7.35 (2H, m), 7.51 (1H, d), MS(EI)m/z 352 is 350((M+)+1).
Elemental analysis values C13H11BrN4 OS
Theoretical value (%) C, 44.46, H, 3.16, N, 15.95,
Measured value (%) C, 44.65, H, 3.11,N, 15.94..

(0139)

Step 2

Synthesis of 5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-thienyl)-1H-tetrazole

5-(5-bromo-2-thienyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and continuing, de-4-methoxybenzylation reaction was carried out in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 252-257°C (recrystallization solvent = chloroform-n-hexane), IR ÉÀ max cm-1,2976, 2200, 1566, 1510.
NMR (400 MHz, DMSO-d6) δ ppm1.84-2.34 (6H, m), 3.62-3.71 (1H, m), 7.44 (1H, d), 7.52 (1H, s), 7.55 (1H, d), MS(FAB)m/z 314 (M+ +1).
Elemental analysis values C14H11N5 S2/1 /2 H2 O
Theoretical value (%) C, 52.15, H, 3.75, N, 21.72,
Measured value (%) C, 52.15, H, 3.67, N, 21.91..

(0140)

Example 19

5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-furyl)-1H-tetrazole :

Step 1

Synthesis of 5-(5-bromo-2-furyl)-1-(4-methoxybenzyl)-1H-tetrazole and 5-(5-bromo-2-furyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(5-bromo-2-furyl)-1H-tetrazole is treated in the same way as in Step 3 of Example 1, and two kinds of isomers are separated by column chromatography using silica gel, and instrument data of 5-(5-bromo-2-thienyl)-1-(4-methoxybenzyl)-1H-tetrazole is as follows.
mp. 70-71°C (it is crystallised at n-hexane).
NMR (400 MHz, CDCl3) δ ppm3.79 (3H, s), 5.72 (2H, s), 6.46 (1H, d), 6.87-6.91 (2H, m), 7.05 (1H, d), 7.36-7.38 (2H, m), MS(EI)m/z 337((M+ +2) +1), 335((M+) +1).

Elemental analysis values C13H11BrN4 O2
Theoretical value (%) C, 46.58, H, 3.31, N, 16.72,
Measured value (%) C, 46.66, H, 3.33, N, 16.89.
data of 5-(5-bromo-2-thienyl)-2-(4-methoxybenzyl)-2H-tetrazole are as follows.
mp. 113-114°C (recrystallization solvent = chloroform-n-hexane).
NMR (400 MHz, CDCl3) δ ppm3.78 (3H, s), 5.76 (2H, s), 6.55 (1H, d), 6.84-6.88 (2H, m), 7.18 (1H, d), 7.27-7.31 (2H, m),
MS(EI)m/z 337 is 335((M+)+1).
Elemental analysis values C13H11BrN4 O2
Theoretical value (%) C, 46.58, H, 3.31, N, 16.72,
Measured value (%) C, 46.69, H, 3.33, N, 16.93..

(0141)

Step 2

Synthesis of 5-(5-iodo-2-furyl)-1-(4-methoxybenzyl)-2H-tetrazole

5-(5-bromo-2-thienyl)-1-(4-methoxybenzyl)-2H-tetrazole 833 mg, potassium iodide 3.98gand cuprous iodide 2.29 g in DMF 20 ml under nitrogen gas stream was heated under reflux. After cooling, the reaction liquor was discharged into water 200 ml, and precipitated crystals were recovered by filtration. Precipitated crystals was suspended in chloroform, and it was dewatered with magnesium sulfate, and thereafter the solvent was eliminated by distillation. The residue was purified by column chromatography (eluate = chloroform : n-hexane = 1: 1) using silica gel, and 5-(5-iodo-2-furyl)-1-(4-methoxybenzyl)-2H-tetrazole 88 mg was obtained as straw-coloured crystalline powder.
mp. 103-105°C (it is crystallised at n-hexane), NMR (400 MHz, CDCl3) δ ppm3.79 (3H, s), 5.72 (2H, s), 6.69 (1H, d), 6.87-6.91 (2H, m), 7.00 (1H, d), 7.36-7.38 (2H, m).

(0142)

Step 3

Synthesis of 5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-thienyl)-1H-tetrazole

5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-furyl)-1-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-furyl)-1-(4-methoxybenzyl)-2H-tetrazole was obtained as straw-coloured crystalline powder.
mp. 107-108°C.
NMR (400 MHz, CDCl3) δ ppm1.88-2.10 (2H, m), 2.26-2.41 (4H, m), 3.64-3.73 (1H, m), 3.80 (3H, s), 5.74 (2H, s), 6.89 (1H, d), 6.89-6.92 (2H, m), 6.99 (1H, s), 7.14 (1H, d), 7.37-7.41 (2H, m).

(0143)

Step 4

Synthesis of 5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-furyl)-1H-tetrazole

5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-furyl)-1-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 164-166°C (recrystallization solvent = chloroform-n-hexane).

NMR (400 MHz, DMSO-d6) δ ppm1.86-2.34 (6H, m), 3.64-3.73 (1H, m), 7.41 (1H, d), 7.43 (1H, d), 7.64 (1H, s), MS(FAB)m/z 298 (M+ +1).

Elemental analysis values C14H11N5 OS

Theoretical value (%) C, 56.55, H, 3.73, N, 23.56,

Measured value (%) C, 56.22, H, 3.81, N, 23.86..

(0144)

Example 20

5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-3-pyridyl)-1H-tetrazole :

Step 1

Synthesis of 3-bromo-5-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) pyridine.

3-bromo-5-(1H-5-tetrazolyl) pyridine was treated in the same way as in Step 3 of Example 1, and 3-bromo-5-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) pyridine was obtained.

mp. 113-115°C (recrystallization solvent = chloroform-n-hexane).

NMR (400 MHz, CDCl3) δ ppm3.80 (3H, s), 5.76 (2H, s), 6.90-6.93 (2H, m), 7.38-7.40 (2H, m), 8.55 (1H, t), 8.75 (1H, d), 9.26 (1H, d).

Elemental analysis values C14H12BrN5 O

Theoretical value (%) C, 48.57, H, 3.49, N, 20.23,

Measured value (%) C, 48.48, H, 3.40, N, 20.30..

(0145)

Step 2

Synthesis of 3-iodo-5-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) pyridine

5-(5-bromo-2-thienyl)-1-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Example 19, and 3-iodo-5-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) pyridine was obtained.

mp. 123-125°C (recrystallization solvent = chloroform-n-hexane).

NMR (400 MHz, CDCl3) δ ppm3.81 (3H, s), 5.76 (2H, s), 6.90-6.93 (2H, m), 7.39-7.41 (2H, m), 8.74 (1H, t), 8.80 (1H, d), 9.28 (1H, d).

(0146)

Step 3

Synthesis of 5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-3-pyridyl)-1H-tetrazole

3-iodo-5-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) pyridine was treated in the same way as in Step 4 of Example 1 with 4-cyclobutyl-2-ethinyl thiazole, and continuing, it was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 113-115°C (recrystallization solvent = chloroform).

NMR (400 MHz, CDCl3) δ ppm1.87-2.33 (6H, m), 3.65-3.73 (1H, m), 7.57 (1H, s), 8.43 (1H, t), 8.73 (1H, d), 9.20 (1H, d), MS(FAB)m/z 309 (M+ +1).

Elemental analysis values C15H12N6 S

Theoretical value (%) C, 58.43, H, 3.92, N, 27.25,

Measured value (%) C, 58.44, H, 3.68, N, 27.25..

(0147).

(Example 21). 5-(6-[2-(4-cyclobutyl-2-thiazolyl] ethinyl)-2-pyridyl)-1H-tetrazole =. Step 1.

Synthesis of 6-bromo-2-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl) pyridine and 6-bromo-2-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) pyridine

6-bromo-2-(1H-5-tetrazolyl) pyridine was treated in the same way as in Step 3 of Example 1, and 6-bromo-2-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl) pyridine and 6-bromo-2-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) pyridine were obtained as mixture of about 2= 3.

NMR (400 MHz, CDCl3) δ ppm3.76 and 3.79 (3H, each s), 5.79 and 6.10 (2H, eachs), 6.83 and 6.89 (2H, d), 7.40 and 7.44 (2H, each d), 7.57-7.75 (2H, m), 8.17 and 8.30 (1, d).

(0148)

Step 2

Synthesis of 6-iodo-2-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl) pyridine and 6-iodo-2-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) pyridine

The aforesaid bromo body was treated in the same way as in Step 2 of Example 19, and 6-iodo-2-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl) pyridine and 6-iodo-2-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) pyridine were obtained as mixture of about 3 : 2.

NMR (400 MHz, CDCl3) δ ppm3.76 and 3.79 (3H, each s), 5.79 and 6.09 (2H, eachs), 6.83 and 6.89 (2H, each d), 7.39 and 7.44 (2H, each d), 7.38-7.52 (1H, m), 7.78-7.86 (1H, m), 8.17 and 8.30 (1H, d).

(0149)

Step 3

Synthesis of 5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-pyridyl)-1-(4-methoxybenzyl)-1H-tetrazole and 5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-pyridyl)-2-(4-methoxybenzyl)-2H-tetrazole

The aforesaid iodine body was treated in the same way as in Step 4 of Example 1, and 5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-pyridyl)-1-(4-methoxybenzyl)-1H-tetrazole and 5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-pyridyl)-2-(4-methoxybenzyl)-2H-tetrazole were obtained as mixture of 1-position and 2 position in a 3 : 2 ratio.

NMR (400 MHz, CDCl3) δ ppm1.88-2.10 (2H, m), 2.27-2.45 (4H, m), 3.70 (1H, m), 3.75 and 3.79 (3H, each s), 5.81 and 6.15 (2H, each s), 6.82 and 6.89 (2H, each d), 7.02 and 7.08 (1H, each s), 7.41 and 7.49 (2H, each d), 7.68-7.72 (1H, m), 7.84-7.92 (1H, m), 8.22 and 8.32 (1H, each d).

Elemental analysis values C23H20N6 OS

Theoretical value (%) C, 64.47, H, 4.70, N, 19.61,

Measured value (%) C, 64.36, H, 4.76, N, 19.78..

(0150)

Step 4

Synthesis of 5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-pyridyl)-1H-tetrazole

Compound of the aforesaid Step 3 was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 162-168°C (ether-n-hexane = recrystallization solvent).

NMR (400 MHz, DMSO-d6) δ ppm1.88-2.13 (2H, m), 2.34-2.42 (4H, m), 3.72 (1H, m), 7.60 (1H, s), 7.68 (1H, d), 7.94 (1H, t), 8.10 (1H, d).

(0151)

Example 22

5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-benzothiazolyl)-1H-tetrazole :

Step 1

Synthesis of 6-acetoxy-2-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl) benzothiazole.

6-acetoxy-2-(1H-tetrazol-5-yl) benzothiazole was treated in the same way as in Step 3 of Example 1, and 6-acetoxy-2-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzothiazole was obtained.

mp. 144-148°C (crystalline powder).

IR ÉÀ max cm-11754.

NMR (400 MHz, CDCl3) δ ppm2.36 (3H, s), 3.80 (3H, s), 5.80 (2H, s), 6.91 (2H, d), 7.28 (2H, d), 7.44 (1H, d), 7.74 (1H, d), 8.19 (1H, d), MS(FAB)m/z 382 (M+ +1).

Elemental analysis values C18H15N5 O3 S

Theoretical value (%) C, 56.68, H, 3.96, N, 18.36,

Measured value (%) C, 56.73, H, 4.04, N, 18.55..

(0152)

Step 2

Synthesis of 6-hydroxy-2-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl) benzothiazole

6-acetoxy-2-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl) benzothiazole 668 mg was dissolved in THF20ml, and 0.25N sodium hydroxide aqueous solution 10 ml were added, and the mixture was stirred at room temperature for four hours. The reaction liquor was discharged into 0.2N hydrochloric acid 300 ml, and the precipitated crystals were recovered by filtration and, after washing with water, were dried, and 6-hydroxy-2-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl) benzothiazole 594 mg was obtained as a yellow powder.

mp. 177-180°C (crystalline powder).

NMR (400 MHz, DMSO-d6) δ ppm3.75 (3H, s), 5.98 (2H, s), 6.98 (2H, d), 7.07 (2H, dd), 7.44 (2H, d), 7.50 (1H, d), 7.96 (1H, d), 10.13 (1H, s), MS(FAB)m/z 340 (M+ +1).

Elemental analysis values C16H13N5 O2 S

Theoretical value (%) C, 56.63, H, 3.86, N, 20.64,

Measured value (%) C, 56.26, H, 3.98, N, 20.31..

(0153)

Step 3

Synthesis of 2-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl) benzothiazol-5-yl) trifluoromethane sulphonate

6-hydroxy-2-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl) benzothiazole 594 mg and ethyl diisopropylamine 1 ml were dissolved in methylene chloride 10 ml, and trifluoromethane sulfonic acid anhydride 0.44 ml were added with stirring at-78°C. The reaction liquor was stirred at room temperature furthermore for 15 hours, and thereafter, it was discharged into 0.2N hydrochloric acid 250 ml, and extraction was carried out with ethyl acetate. The extract was washed with 1N hydrochloric acid and saturated aqueous sodium chloride solution and thereafter, were dried with magnesium sulfate. The residue obtained by the elimination of the solvent by distillation was purified by column chromatography (eluate = n-hexane-ethyl acetate = 5 : 1) using silica gel, and 2-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl) benzothiazol-5-yl) trifluoromethane sulphonate 546 mg was obtained as powder.

mp. 115-116°C.

NMR (400 MHz, CDCl3) δ ppm3.80 (3H, s), 5.85 (2H, s), 6.91 (2H, d), 7.45 (2H, d), 7.47 (1H, dd), 7.93 (1H, d), 8.27 (1H, d), MS(FAB)m/z 472 (M+ +1).

Elemental analysis values C17H12F3 N5 O4 S2

Theoretical value (%) C, 43.31, H, 2.57, N, 14.86,

Measured value (%) C, 43.58, H, 2.68, N, 15.11..

(0154)

Step 4

Synthesis of 5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzothiazol-5-yl)-1-(4-methoxybenzyl)-1H-tetrazole

Triethylamine 0.2ml and DMF5ml was added to 2-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl) benzothiazol-5-yl) trifluoromethane sulphonate 471 mg, cuprous iodide 19 mg and bis (triphenyl phosphine) palladium (2) dichloride 35 mg, and it was stirred under a stream of nitrogen at room temperature for one hour. 4-cyclobutyl-2-ethinyl thiazole 245 mg was added to the reaction liquor and the mixture was stirred at 90°C for four hours. After cooling, the reaction liquor was discharged into 1N hydrochloric acid 250 ml and extraction was carried out with ethyl acetate. The liquid extract was washed with saturated aqueous sodium chloride solution, and thereafter, drying with magnesium sulfate was carried out. The residue obtained by the elimination of the solvent by distillation was purified by column chromatography (eluate = n-hexane-ethyl acetate = 4 : 1) using silica gel, and 5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzothiazol-5-yl)-1-(4-methoxybenzyl)-1H-tetrazole 308 mg was obtained as needle crystals.

mp. 161°C.

NMR (400 MHz, CDCl3) δ ppm1.91-2.12 (2H, m), 2.28-2.43 (4H, m), 3.71 (1H, m), 3.80 (3H, s), 5.83 (2H, s), 6.91 (2H, d), 6.99 (1H, s), 7.45 (2H, d), 7.74 (1H, dd), 8.19 (1H, d), 8.21 (1H, d).

(0155)

Step 5

Synthesis of 5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-benzothiazolyl)-1H-tetrazole

5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzothiazol-5-yl)-1-(4-methoxybenzyl)-1H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained as a yellow powder.

mp. 225-227°C (recrystallization solvent = chloroform).

NMR (400 MHz, DMSO-d6) δ ppm1.90-2.04 (2H, m), 2.22-2.32 (4H, m), 3.69 (1H, m), 7.57 (1H, s), 7.89 (1H, d), 8.25 (1H, d), 8.65 (1H, s), MS(FAB)m/z 365 (M+ +1).

Elemental analysis values C17H12N6 S2

Theoretical value (%) C, 56.03, H, 3.32, N, 23.06,

Measured value (%) C, 55.79, H, 3.35, N, 23.06..

(0156)

Example 23

5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-benzoxazolyl)-1H-tetrazole :

Step 1

Synthesis of 5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzo oxazole.

5-iodo-2-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzo oxazole was treated in the same way as in Step 4 of Example 1, and 5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzo oxazole was obtained.

mp. 178-180.

NMR (400 MHz, CDCl3) δ ppm1.92-2.11 (2H, m), 2.28-2.40 (4H, m), 3.71 (1H, m), 3.80 (3H, s), 5.85 (2H, s), 6.92 (2H, d), 6.98 (1H, s), 7.45 (2H, s), 7.76-7.71 (2H, d), 8.10 (1H, s).

(0157)

Step 2

Synthesis of 5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-benzoxazolyl)-1H-tetrazole

5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzo oxazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained as minute needle crystal.

mp. 226-229°C (decomp.).

NMR (400 MHz, DMSO-d6) δ ppm1.84-2.06 (2H, m), 2.20-2.34 (4H, m), 3.68 (1H, m), 7.54 (1H, s), 7.84 (1H, dd), 8.04 (1H, d), 8.29 (1H, d), MS(FAB)m/z 349 (M+ +1).

Elemental analysis values C17H12N6 OS

Theoretical value (%) C, 57.13, H, 3.67, N, 23.52,

Measured value (%) C, 57.55, H, 3.54, N, 23.33..

(0158)

Example 24

7-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-3-(1H-tetrazol-5-yl)-4H-pyrido (1, 2-a) pyrimidin-3-on :

Step 1

Synthesis of 7-bromo-3-(2-[4-methoxybenzyl]-2H-tetrazol-5-yl)-4H-pyrido (1, 2-a) pyrimidin-3-one

2-amino-5-bromopyridine 3.57 g and ethyl 3-dimethylamino-2-(2-(4-(methoxybenzyl)-2H-tetrazol-5-yl) acrylic acid 7.94 g were heated under reflux for three days in propionic acid 30 ml. The reaction liquor was discharged into water 300 ml, and the precipitated crystals were recovered by filtration and, after washing with water, were dried. This was purified by column chromatography (eluate = chloroform = methanol = 200 : 1) using silica gel, and crystalline powder did 7-bromo-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-4H-pyrido (1, 2-a) pyrimidin-3-on 4.03 g, and it was obtained.

mp. 172-175°C.

IR ÉÀ max cm-11706.

NMR (400 MHz, CDCl3) δ ppm3.79 (3H, s), 5.82 (2H, s), 6.88-6.91 (2H, m), 7.41-7.43 (2H, m), 7.67 (1H, d), 7.90 (1H, dd), 9.22 (1H, s), 9.38 (1H, d), MS(EI)m/z 414), 412((M+) +1)).
Elemental analysis values C17H13BrN6 O2
Theoretical value (%) C, 49.41, H, 3.17, N, 20.34,
Measured value (%) C, 49.24, H, 3.24, N, 20.39..

(0159)

Step 2

Synthesis of 7-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-3-(1H-tetrazol-5-yl)-4H-pyrido (1, 2-a) pyrimidin-3-one

7-bromo-3-(2-[4-methoxybenzyl]-2H-tetrazol-5-yl)-4H-pyrido (1, 2-a) pyrimidin-3-on 413 mg, 4-cyclobutyl-2-ethinyl thiazole 163 mg, palladium acetate (2) 22 mg and triphenyl phosphine 52 mg were heated under reflux for four hours in triethylamine 20 ml. The reaction liquor was concentrated and chloroform 50 ml were added and were successively washed with 1N hydrochloric acid, water, saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution and next were dried with sodium sulfate. the solvent was eliminated by distillation, and the residue was purified by column chromatography (eluate = chloroform : methanol = 200 : 1) using silica gel, and thereafter the obtained coupled product was treated in the same way as in Step 5 of Example 1 without purification, and the title substance 105 mg was obtained as straw-coloured crystalline powder.
mp. >300°C (recrystallization solvent = chloroform-n-hexane).
IR ÉÀ maxcm-11706.
NMR (400Mz, DMSO-d6) δ ppm1.84-2.32 (6H, m), 3.65-3.73 (1H, m), 7.61 (1H, s), 7.80 (1H, d), 8.09 (1H, d), 8.94 (1H, br s), 9.34 (1H, s), MS(FAB)m/z 376 (M+ +1).
Elemental analysis values C18H13N7 OS
Theoretical value (%) C, 57.59, H, 3.49, N, 26.12,
Measured value (%) C, 57.95, H, 3.40, N, 25.93..

(0160)

Example 25

5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-benzo (b) thienyl)-1H-tetrazole :

Step 1

Synthesis of 5-(5-bromo-2-benzo (b) thienyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(5-bromo-2-benzo (b) thienyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(5-bromo-2-benzo (b) thienyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.
mp. 140-142°C (recrystallization solvent = chloroform-n-hexane).

IR ÉÀ max cm-13080, 2840, 1614, 1584, 1538, 1516.
NMR (400Mz, CDCl3) δ ppm3.81 (3H, s), 5.75 (2H, s), 6.90-6.93 (2H, m), 7.39-7.41 (2H, m), 7.48 (1H, dd), 7.73 (1H, d), 7.96 (1H, s), 7.98 (1H, d), MS(EI)m/z 402 402((M+) +1).
Elemental analysis values C17H13BrN4 OS
Theoretical value (%) C, 50.88, H, 3.27, N, 13.96,
Measured value (%) C, 50.57, H, 3.27, N, 13.91..

(0161)

Step 2

Synthesis of 5-(5-iodo-2-benzo (b) thienyl)-2-(4-methoxybenzyl)-2H-tetrazole
5-(5-bromo-2-benzo (b) thienyl)-1H-tetrazole was treated in the same way as in Step 2 of Example 19, and 5-(5-iodo-2-benzo (b) thienyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.
mp. 131-134°C (recrystallization solvent = chloroform-n-hexane).
NMR (400Mz, CDCl3) δ ppm3.80 (3H, s), 5.75 (2H, s), 6.90-6.92 (2H, m), 7.39-7.41 (2H, m), 7.66-7.60 (2H, m), 7.94 (1H, s), 8.19 (1H, s).

(0162)

Step 3

Synthesis of 5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-benzo (b) thienyl)-1H-tetrazole
5-(5-iodo-2-benzo (b) thienyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and de-4-methoxybenzylation of Step 5 of Example 1 were carried out with the obtained coupled product without purification, and the title substance was obtained.
mp. 241-244°C (recrystallization solvent = chloroform-ethanol).
IR ÉÀ max cm-12208, 1584, 1532, 1504.
NMR (400Mz, DMSO-d6) δ ppm1.85-2.34 (6H, m), 3.64-3.73 (1H, m), 7.54 (1H, s), 7.71 (1H, dd), 8.20 (1H, s), 8.24 (1H, d), 8.41 (1H, s), MS(FAB)m/z 364 (M+ +1).
Elemental analysis values C18H13N5 S2
Theoretical value (%) C, 59.48, H, 3.60, N, 19.27,
Measured value (%) C, 59.21, H, 3.70, N, 19.31..

(0163)

Example 26

5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-oxo-2H-benzopyran-3-yl)-1H-tetrazole =. Step 1.
Synthesis of 5-(5-bromo-2-oxo-2H-benzopyran-3-yl)-1-(4-methoxybenzyl)-1H-tetrazole and 5-(5-bromo-2-oxo-2H-benzopyran-3-yl)-2-(4-methoxybenzyl)-2H-tetrazole

5-(5-bromo-2-oxo-2H-benzopyran-3-yl)-1H-tetrazole is treated in the same way as in Step 3 of Example 1 and 5-(5-bromo-2-oxo-2H-benzopyran-3-yl)-1-(4-methoxybenzyl)-1H-tetrazole and 5-(5-bromo-2-oxo-2H-benzopyran-3-yl)-2-(4-methoxybenzyl)-2H-tetrazole were obtained as a 1 position and 2-position mixture.

IR ÉÀ max cm-12840, 1750, 1722, 1614, 1606, 1568, 1516.

NMR (400Mz, CDCl3) δ ppm3.68 and 3.80 (3H, each s), 5.76 (1H, s), 5.81 (1H, s), 6.71-6.74 (1H, m), 6.89-6.92 (1H, m), 7.06-7.08 (1H, m), 7.29 and 7.31 (1H, each d), 7.40-7.42 (1H, m), 7.65, 7.70, 7.75 and 7.76 (2H, each m), 7.99 (1/2 H, s), 8.58 (1/2 H, s), MS(FAB)m/z 414((M+ +2) +1), 412((M+) +1).

Elemental analysis values C18H13N4 BrO3

Theoretical value (%) C, 52.32, H, 3.17, N, 13.56,

Measured value (%) C, 51.93, H, 3.24, N, 13.38..

(0164)

Step 2

Synthesis of 5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-oxo-2H-benzopyran-3-yl)-1H-tetrazole

The aforesaid bromo body and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and the obtained coupled product was treated in the same way as in Step 5 of Example 1 without purification, and the title substance was obtained.

mp. >300°C (recrystallization solvent = chloroform-n-hexane).

IR ÉÀ maxcm-12980, 2944, 2216, 1742, 1708, 1622, 1606, 1578, 1504.

NMR (400Mz, CDCl3) δ ppm1.87-2.33 (6H, m), 3.63-3.72 (1H, m), 7.51 (1H, d), 7.54 (1H, s), 7.85 (1H, dd), 8.20 (1H, d), 8.53 (1H, s), MS(FAB)m/z 376 (M+ +1).

Elemental analysis values C19H13N5 O2

Theoretical value (%) C, 60.79, H, 3.49, N, 18.66,

Measured value (%) C, 60.47, H, 3.52, N, 18.61..

(0165)

Example 27

5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-benzo (b) furyl)-1H-tetrazole :

Step 1

Synthesis of 5-(5-bromo-2-benzo (b) furyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(5-bromo-2-benzo (b) furyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(5-bromo-2-benzo (b) furyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 143-145°C (recrystallization solvent = chloroform-ether).

NMR (400Mz, CDCl3) δ ppm3.79 (3H, s), 5.78 (2H, s), 6.90 (2H, d), 7.41 (2H, d), 7.43 (1H s), 7.47 (1H, s), 7.79 (1H, s).

(0166)

Step 2

Synthesis of 5-(5-iodo-2-benzo (b) furyl)-2-(4-methoxybenzyl)-2H-tetrazole

5-(5-bromo-2-benzo (b) furyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 2 of Example 19, and 5-(5-iodo-2-benzo (b) furyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 136-138°C (recrystallization solvent = ether-hexane).

NMR (400Mz, CDCl3) δ ppm3.80 (3H, s), 5.78 (2H, s), 6.90 (2H, d), 7.37 (1H, d), 7.41 (1H s), 7.41 (1H, d), 7.63 (1H, dd), 8.00 (1H, d).

(0167)

Step 3

Synthesis of 5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-benzo (b) furyl)-2-(4-methoxybenzyl)-2H-tetrazole

5-(5-iodo-2-benzo (b) furyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-benzo (b) furyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 154-155°C (recrystallization solvent = chloroform-ether).

NMR (400Mz, CDCl3) δ ppm1.89-2.11 (2H, m), 2.28-2.43 (4H, m), 3.70 (1H, m) .3.80 (3H, s), 5.79 (2H, s), 6.91 (2H, d), 6.95 (1H, s), 7.42 (2H, d), 7.49 (1H, s), 7.60 (2H, s), 7.92 (1H, s).

(0168)

Step 4

Synthesis of 5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-benzo (b) furyl)-1H-tetrazole

5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-benzo (b) furyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 207-212°C (recrystallization solvent = ethanol-chloroform-n-hexane).

IR ÉÀ max cm-12216.

NMR (400Mz, DMSO-d6) δ ppm1.85-2.06 (2H, m), 2.19-2.52 (4H, m), 3.68 (1H, m) .7.53 (1H, s), 7.74 (1H, d), 7.77 (1H, s), 7.88 (1H, d), 8.16 (1H, s).

Elemental analysis values C18H13N5 OS

Theoretical value (%) C, 62.23, H, 3.77, N, 20.16,

Measured value (%) C, 61.95, H, 3.96, N, 20.10..

(0169)

Example 28

5-(7-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-oxo-4H-benzopyran-2-yl) carboxylic acid :

Step 1

Synthesis of ethyl 5-(4-oxo-7-trifluoromethane sulphonyl oxy-4H-benzopyran-2-yl) carboxylate.

Ethyl 5-(7-hydroxy-4-oxo-4H-benzopyran-2-yl) carboxylate was treated in the same way as in Step 3 of Example 22, and ethyl 5-(4-oxo-7-trifluoromethane sulphonyl oxy-4H-benzopyran-2-yl) carboxylate was obtained.

mp. 125-127°C (recrystallization solvent = chloroform-n-hexane), IR ÉÀ max cm-12216.

NMR (400Mz, CDCl3) δ ppm1.45 (3H, t), 4.48 (2H, q), 7.15 (1H, s), 7.37 (1H, dd), 7.59 (1H, d), 8.31 (1H, d).

(0170)

Step 2

Synthesis of ethyl 5-(7-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-oxo-4H-benzopyran-2-yl) carboxylate

Ethyl 5-(4-oxo-7-trifluoromethane sulphonyl oxy-4H-benzopyran-2-yl) carboxylate and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and ethyl 5-(7-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-oxo-4H-benzopyran-2-yl) carboxylate was obtained.

mp. 138-141°C (recrystallization solvent = ether-n-hexane).

NMR (400Mz, CDCl3) δ ppm1.44 (3H, t), 1.91-2.43 (6H, m), 3.68-3.76 (1H, m), 4.47 (2H, q), 7.04 (1H, s), 7.13 (1H, s), 7.61 (1H, dd), 7.82 (1H, d), 8.18 (1H, d).

(0171)

Step 3

Synthesis of 5-(7-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-oxo-4H-benzopyran-2-yl) carboxylic acid

Ethanol 10 ml and water 1 ml were added to 5-(7-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-oxo-4H-benzopyran-2-yl) carboxylate 228 mg and sodium bicarbonate 230 mg, and the mixture was heated under reflux for two hours. After cooling, water 100 ml were added to the reaction liquor, and 1N hydrochloric acid was added, and it was prepared to pH3. The precipitated crystals were recovered by filtration and, after washing with water, were dried. The obtained crude crystals were recrystallised from chloroform-n-hexane, and the title substance 175 mg was obtained as a crystalline powder.

mp. 240-243°C (decomp.).

IR ÉÀ max cm-12216, 1734, 1654.

NMR (400Mz, DMSO-d6) δ ppm1.87-2.32 (6H, m), 3.65-3.73 (1H, m), 6.96 (1H, s), 7.62 (1H, s), 7.76 (1H, d), 8.08 (1H, s), 8.09 (1H, d), MS(FAB)m/z 352 (M+ +1).

Elemental analysis values C19H13NO4 S/1 /4 H2 O

Theoretical value (%) C, 64.12, H, 3.82, N, 3.94,
Measured value (%) C, 64.29, H, 3.83, N, 3.81..

(0172).

Example 29

5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-3-benzo (b) thienyl)-1H-tetrazole:

Step 1

Synthesis of 5-(5-iodo-3-benzo (b) thienyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(5-iodo-3-benzo (b) thienyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(5-iodo-3-benzo (b) thienyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.
mp. 134-136°C (recrystallization solvent = chloroform - n-hexane).
NMR (400 Mz, CDCl3) δ ppm 3.80 (3H, s), 5.80 (2H, s), 6.91-6.94 (2H, m), 7.42-7.45 (2H, m), 7.64 (1H, d), 7.70 (1H, dd), 8.27 (1H, s), 9.09 (1H, d).

(0173)

Step 2

Synthesis of 5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-3-benzo (b) thienyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(5-iodo-3-benzo (b) thienyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-3-benzo (b) thienyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as brown oily substance.
NMR (400Mz, CDCl3) δ ppm 1.95-2.12 (2H, m), 2.30-2.41 (4H, m), 3.67-3.75 (1H, m), 3.79 (3H, s), 5.83 (2H, s), 6.91-6.93 (2H, m), 7.44-7.46 (2H, m), 7.62 (1H, dd), 7.89 (1H, d), 8.37 (1H, s), 8.99 (1H, d).

(0174)

Step 3

Synthesis of 5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-3-benzo (b) thienyl)-1H-tetrazole.

5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-3-benzo (b) thienyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 125-127°C (recrystallization solvent = chloroform - n-hexane).
IR v max cm-1 2212. NMR (400Mz, DMSO-d6) δ ppm 1.90-2.08 (2H, m), 2.28-2.32 (4H, m), 3.64-3.72 (1H, m), 7.54 (1H, s), 7.75 (1H, dd), 8.28 (1H, d), 8.67 (1H, s), 8.93 (1H, d),
MS(FAB)m/z 364 (M+ +1).
Elemental analysis value,

Theoretical value (%) of C18H13N5S2, C, 59.48, H, 3.61, N, 19.27,
Measured values (%) C, 59.44, H, 3.40, N, 17.13..

(0175)

Example 30

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-5-benzo (b) thienyl)-1H-tetrazole:

Step 1

Synthesis of 5-(3-iodo-5-benzo (b) thienyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-5-benzo (b) thienyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(3-iodo-5-benzo (b) thienyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.
mp. 155-157°C (recrystallization solvent = chloroform - n-hexane). NMR (400Mz, CDCl3) δ ppm 3.80 (3H, s), 5.77 (2H, s), 6.90-6.93 (2H, m), 7.41-7.43 (2H, m), 7.67 (1H, s), 7.94 (1H, d), 8.16 (1H, d), 8.52 (1H, s).

(0176)

Step 2

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-5-benzo (b) thienyl)-1H-tetrazole.

5-(3-iodo-5-benzo (b) thienyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and continuing, debenzylation reaction was carried out in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 195-197°C (recrystallization solvent = chloroform - n-hexane).
IR v max cm-1 2212. NMR (400Mz, DMSO-d6) δ ppm 1.88-2.05 (2H, m), 2.21-2.36 (4H, m), 3.67-3.75 (1H, m), 7.60 (1H, s), 8.16 (1H, d), 8.38 (1H, d), 8.58 (1H, s), 8.62 (1H, s),
MS(FAB)m/z 364 (M+ +1).
Elemental analysis value,
Theoretical value (%) of C18H13N5S2 • H2O, C, 58.04, H, 3.79, N, 18.80,
Measured values (%) C, 58.28, H, 3.56, N, 18.67..

(0177)

Example 31

5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)-1H-tetrazole:

Step 1

Synthesis of N-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl)-2-amino-5-iodo-benzamide and N-(2-(4-methoxybenzyl)-2-H-tetrazol-5-yl)-2-amino-5-iodo-benzamide.

N-(1H-tetrazol-5-yl)-2-amino-5-iodo-benzamide was treated in the same way as in Step 3 of Example 1, and N-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl)-2-amino-5-iodo-benzamide and N-(2-(4-methoxybenzyl)-2-H-tetrazol-5-yl)-2-amino-5-iodo-benzamide were obtained as an oily substance.

NMR (400 MHz, CDCl3) δ ppm 3.75 (3H s), 5.80 (2H, s), 6.61 (1H, d), 6.70-6.80 (2H, br), 6.93 (2H, d), 7.39 (2H, d), 7.50 (1H d), 7.97 (1H, br s), 8.02 (1H, d).

(0178)

Step 2

Synthesis of 5-(6-iodo-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)-2-(4-methoxybenzyl)-2H-tetrazole.

The aforesaid iodine body 1.4 g were dissolved in DMF 10 ml and 1,1'-carbonyldiimidazole 0.62 g were added and the mixture was stirred at 80°C for two hours. After cooling, the reaction liquor was discharged into 1N hydrochloric acid 100 ml and extraction was carried out with ethyl acetate. The liquid extract was washed with saturated aqueous sodium chloride solution and thereafter, was dried with sodium sulfate. The residue obtained by elimination by distillation of the solvent was purified by column chromatography (eluate = n-hexane - ethyl acetate = 2 : 1) using silica gel, and 5-(6-iodo-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as a yellow oily substance.

NMR (400 MHz, CDCl3) δ ppm 3.82 (3H s), 5.79 (2H, s), 6.63 (2H, dd), 6.70-6.80 (1H, m), 7.10 (2H, d), 7.38 (1H, d), 7.89 (1H dd), 8.31 (1H, d).

(0179)

Step 3

Synthesis of 5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(6-iodo-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as brown oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.90-2.00 (1H, m), 2.00-2.10 (1H, m), 2.20-2.40 (4H, m), 3.61 (3H, s), 3.60-3.70 (1H, m), 5.79 (2H, s), 6.65 (2H, d), 7.00 (1H, s), 7.00-7.10 (1H, m), 7.12 (2H, d), 7.37 (1H, d), 7.77 (1H, dd), 8.21 (1H, d).

(0180)

Step 4

Synthesis of 5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)-1H-tetrazole.

5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. >300°C. NMR (400 MHz, DMSO-d6) δ ppm 1.80-1.90 (1H, m), 1.90-2.10 (1H, m), 2.20-2.40 (4H, m), 3.60-3.70 (1H, m), 7.32 (1H, d), 7.52 (1H, s), 7.50-7.60 (1H, br), 7.99 (1H, dd), 8.13 (1H, d), 12.10 (1H, br),

MS(FAB)m/z 392 (M+ +1).

Elemental analysis value,

Theoretical value (%) of C18H13N7O2S • 3/2 H2O, C, 55.38,H, 4.13, N, 17.94,

Measured values (%) C, 55.59, H, 3.86, N, 17.78..

(0181)

Example 32

5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-oxo-3,4-dihydroquinazolin-3-yl)-1H-tetrazole:

Step 1

Synthesis of 5-(6-iodo-4-oxo-3,4-dihydroquinazolin-3-yl)-2-(4-methoxybenzyl)-2H-tetrazole.

Ortho ethyl formate 1.8 ml were added to mixture 200 mg of N-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl)-2-amino-5-iodo-benzamide and N-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-amino-5-iodo-benzamide, and it was heated with stirring for eight hours. The residue obtained by the concentration of the reaction liquor was purified by column chromatography (eluate = n-hexane : ethyl acetate = 2 : 1) using silica gel, and 5-(6-iodo-4-oxo-3,4-dihydroquinazolin-3-yl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as an oily substance.

NMR (400 MHz, CDCl3) δ ppm 3.81 (3H, s), 5.80 (2H, s), 6.93 (2H, dd), 7.43 (2H, d), 7.50 (1H, d), 8.10 (1H, dd), 8.27 (1H, s), 8.69 (1H, d).

(0182)

Step 2

Synthesis of 5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl-4-oxo-3,4-dihydroquinazolin-3-yl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(6-iodo-4-oxo-3,4-dihydroquinazolin-3-yl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl-4-oxo-3,4-dihydroquinazolin-3-yl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as brown oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.90-2.00 (1H, m), 2.00-2.10 (1H, m), 2.20-2.40 (4H, m), 3.61 (3H, s), 3.60-3.70 (1H, m), 5.79 (2H, s), 6.65 (2H, d), 7.00 (1H, s), 7.43 (2H, d), 7.50 (1H, d), 8.10 (1H, dd), 8.27 (1H, s), 8.69 (1H, d).

(0183)

Step 3

Synthesis of 5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-oxo-3,4-dihydroquinazolin-3-yl)-1H-tetrazole.

5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl-4-oxo-3,4-dihydroquinazolin-3-yl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 189-190°C (recrystallization solvent : chloroform - ethanol).

IR v max cm-1 1956, 1886, 1550, 1290, 1048. NMR (400 MHz, DMSO-d6) δ ppm 1.80-1.90 (1H, m), 1.90-2.00 (1H, m), 2.20-2.40 (4H, m), 3.50-3.60 (1H, m), 7.52 (1H, s), 7.84 (1H, d), 8.10 (1H, s), 8.25 (1H, dd), 8.39 (1H, d), 12.60 (1H, br s),

MS(FAB)m/z 394 (M+ +1).

(0184)

Example 33

5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-oxo-3H-triazin-3-yl)-1H-tetrazole:

Step 1

Synthesis of 5-(6-iodo-4-oxo-3H-triazin-3-yl)-2-(4-methoxybenzyl)-2H-tetrazole.

5.3 % sulfuric acid 1.2 ml and ethanol 0.2 ml were added to mixture 300 mg of N-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl)-2-amino-5-iodo benzamide and N-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-amino-5-iodo benzamide, and sodium nitrite 56 mg was added at 0-5°C, and the mixture was stirred for four hours. The reaction liquor was poured into iced water 100 ml, and precipitated crystals were recovered by filtration and, after washing with water, were dried, and 5-(6-iodo-4-oxo-3H-triazin-3-yl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as yellow caramel state oily substance.

NMR (400 MHz, CDCl3) δ ppm 3.76 (3H, s), 6.04 (2H, s), 6.99 (2H, dd), 7.45 (2H, d), 8.07 (1H, d), 8.52 (1H, dd), 8.59 (1H, d).

(0185)

Step 2

Synthesis of 5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-oxo-3H-triazin-3-yl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(6-iodo-4-oxo-3H-triazin-3-yl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-oxo-3H-triazin-3-yl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as brown oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.90-2.00 (1H, m), 2.00-2.10 (1H, m), 2.20-2.40 (4H, m), 3.61 (3H, s), 3.60-3.70 (1H, m), 6.04 (2H, s), 7.00 (1H, s), 7.12 (2H, dd), 7.20 (2H, d), 8.07 (1H, d), 8.60 (1H, dd), 8.63 (1H, d).

(0186)

Step 3

Synthesis of 5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-oxo-3H-triazin-3-yl)-1H-tetrazole.

5-(6-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-oxo-3H-triazin-3-yl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 189-190°C (recrystallization solvent = water - ethanol).

IR v max cm-1 1618, 1550, 1394, 1290, 996. NMR (400 MHz, DMSO-d6) δ ppm 1.80-1.90 (1H, m), 1.90-2.00 (1H, m), 2.20-2.40 (4H, m), 3.50-3.60 (1H, m), 7.50 (1H, s), 7.99 (1H, d), 8.55 (1H, dd), 8.58 (1H, d), 12.56 (1H, br s),

MS(FAB)m/z 377 (M+ +1).

Elemental analysis value,

Theoretical value (%) of C17H12N8OS • H2O, C, 51.77, H, 3.58, N, 28.41,

Measured values (%) C, 52.01, H, 3.60, N, 28.79..

(0187)

Example 34

5-(7-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-3-methoxy-benzo[b]thiophen-2-yl)-1H-tetrazole:

Step 1

Synthesis of 5-(7-iodo-3-methoxy-benzo[b]thiophen-2-yl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(7-iodo-3-methoxy-benzo[b]thiophen-2-yl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(7-iodo-3-methoxy-benzo[b]thiophen-2-yl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 156-158°C (recrystallization solvent = chloroform - n-hexane). NMR (400 MHz, CDCl3) δ ppm 3.80 (3H, s), 4.07 (3H, s), 5.77 (2H, s), 6.90-6.92 (2H, m), 7.16 (1H, t), 7.41-7.43 (2H, m), 7.78 (1H, d), 7.87 (1H, d), MS(EI)m/z 478(M+).

Elemental analysis value,

Theoretical value (%) of C18H15IN4O2, C, 45.20, H, 3.16, N, 11.72,

Measured values (%) C, 45.40, H, 3.28, N, 11.48..

(0188)

Step 2

Synthesis of 5-(7-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-3-methoxy-benzo[b]thiophen-2-yl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(7-iodo-3-methoxy-benzo[b]thiophen-2-yl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(7-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-3-methoxy-benzo[b]thiophen-2-yl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as brown oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.95-2.07 (2H, m), 2.31-2.42 (4H, m), 3.68-3.77 (1H, m), 3.80 (3H, s), 4.09 (3H, s), 5.78 (2H, s), 6.89-6.93 (2H, m), 7.01 (1H, s), 7.41-7.45 (2H, m), 7.67 (1H, dd), 7.88 (1H, dd).

(0189)

Step 3

Synthesis of 5-(7-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-3-methoxy-benzo[b]thiophen-2-yl)-1H-tetrazole.

5-(7-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-3-methoxy-benzo[b]thiophen-2-yl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained as orange-brown coloured crystalline powder.

mp. 156-158°C (recrystallization solvent = chloroform - n-hexane). NMR (400 MHz, DMSO-d6) δ ppm 1.88-2.02 (2H, m), 2.24-2.34 (4H, m), 3.67-3.76 (1H, m), 4.16 (3H, s), 7.61-7.65 (2H, m), 7.89 (1H, d), 8.16 (1H, d),

MS(FAB)m/z 394 (M+ +1).

Elemental analysis value,

Theoretical value (%) of C19H15N5 OS2 • 1/4 H2O, C, 57.34, H, 3.93, N, 17.60,

Measured values (%) C, 57.33, H, 3.93, N, 17.49..

(0190)

Example 35

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-fluorophenyl)-1H-tetrazole:

Step 1

Synthesis of 5-(3-iodo-6-fluorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-6-fluorophenyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(3-iodo-6-fluorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 99-101°C (recrystallization solvent = chloroform - n-hexane). NMR (400 MHz, CDCl3) δ ppm 3.80 (3H, s), 5.77 (2H, s), 6.89-6.92 (2H, m), 7.39-7.42 (2H, m), 7.71-7.75 (1H, m), 8.41-8.43 (1H, m).

(0191)

Step 2

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-fluorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-6-fluorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-fluorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 126-128°C (recrystallization solvent = chloroform - n-hexane). NMR (400 MHz, CDCl3) δ ppm 1.89-2.42 (6H, m), 3.66-3.74 (1H, m), 3.80 (3H, s), 5.78 (2H, s), 6.90-6.93 (2H, m), 6.97 (1H, s), 7.21-7.26 (1H, m), 7.41-7.43 (2H, m), 7.63-7.67 (1H, m), 8.35-8.38 (1H, m).

(0192)

Step 3

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-fluorophenyl)-1H-tetrazole.

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-fluorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 223-225°C (decomp) (recrystallization solvent = chloroform - n-hexane).

IR v max cm-1 3080, 2220, 1620, 1556, 1508. NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.35 (6H, m), 3.64-3.72 (1H, m), 7.56 (1H, s), 7.62-7.66 (1H, m), 7.94-7.98 (1H, m), 8.30-8.32 (1H, m), MS(FAB)m/z 326 (M+ +1).

Elemental analysis value,

Theoretical value (%) of C16H12FN5S, C, 59.06, H, 3.72, N, 21.52,

Measured values (%) C, 59.01, H, 3.84, N, 21.76..

(0193)

Example 36

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-methylphenyl)-1H-tetrazole:

Step 1

Synthesis of 5-(3-iodo-4-methylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-4-methylphenyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(3-iodo-4-methylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 136-138°C (recrystallization solvent = ether-n-hexane). NMR (400 MHz, CDCl3) δ ppm 2.74 (3H, s), 3.80 (3H, s), 5.72 (2H, s), 6.90 (2H, d), 7.31 (1H, d), 7.37 (2H, d), 7.99 (1H, dd), 8.77 (1H, d).

(0194)

Step 2

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-methylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-methylphenyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-methylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as brown oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.90-2.11 (2H, m), 2.27-2.43 (4H, m), 2.57 (3H, s), 3.71 (1H, m), 3.80 (3H, s), 5.73 (2H, s), 6.91 (2H, d), 6.97 (1H, s), 7.34 (1H, d), 7.40 (2H, d), 8.04 (1H, dd), 8.32 (1H, d).

(0195)

Step 3

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-methylphenyl)-1H-tetrazole.

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-methylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 180-182°C (recrystallization solvent = water - ethanol). NMR (400 MHz, DMSO-d6) δ ppm 1.91-2.08 (2H, m), 2.22-2.34 (4H, m), 2.57 (3H, s), 3.69 (1H, m), 7.47 (1H, s), 7.57 (1H, d), 8.04 (1H, d), 8.25 (1H, s).

Elemental analysis value,

Theoretical value (%) of C17H15N5S, C, 63.53, H, 4.70, N, 21.79,

Measured values (%) C, 63.30, H, 4.83, N, 20.99..

(0196)

Example 37

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-methoxyphenyl)-1H-tetrazole:

Step 1

Synthesis of 5-(3-iodo-4-methoxyphenyl)-2-(4-(methoxybenzyl)-2H-tetrazole.

5-(3-iodo-4-methoxyphenyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(3-iodo-4-methoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 125-126°C (recrystallization solvent = chloroform - n-hexane). NMR (400 MHz, CDCl3) δ ppm 3.80 (3H, s), 3.93 (3H, s), 5.71 (2H, s), 6.88 (1H, d), 6.91 (2H, d), 7.37 (2H, d), 8.09 (1H, dd), 8.54 (1H, d).

(0197)

Step 2.

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-methoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-4-methoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-methoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 99-100°C (recrystallization solvent = ether-n-hexane). NMR (400 MHz, CDCl3) δ ppm 1.89-2.10 (2H, m), 2.27-2.41 (4H, m), 3.73 (1H, m), 3.80 (3H, s), 3.96 (3H, s), 5.72 (2H, s), 6.91 (2H, d), 6.95 (1H, s), 6.99 (1H, d), 7.39 (2H, d), 8.13 (1H, dd), 8.31 (1H, d).

(0198)

Step 3

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-methoxyphenyl)-1H-tetrazole.

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-methoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 215-217°C (recrystallization solvent = ethanol-ether). NMR (400 MHz, DMSO-d6) δ ppm 1.85-2.06 (2H, m), 2.19-2.34 (4H, m), 3.68 (1H, m), 3.99 (3H, s), 7.40 (1H, d), 7.55 (1H, s), 8.15 (1H, dd), 8.23 (1H, d).

Elemental analysis value,

Theoretical value (%) of C17H15N5OS • 1/4 H2O, C, 58.94, H, 4.66, N, 20.22,

Measured values (%) C, 59.36, H, 4.63, N, 19.90..

(0199)

Example 38

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-hydroxyphenyl)-1H-tetrazole:

Step 1

Synthesis of 5-(3-iodo-6-(4-methoxybenzyl) oxy phenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

2 equivalents of 4-methoxybenzyl chloride and potassium carbonate were used, and 5-(3-iodo-6-hydroxyphenyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(3-iodo-6-(4-methoxybenzyl) oxy phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 159-160°C (recrystallization solvent = chloroform - n-hexane). NMR (400 MHz, CDCl3) δ ppm 3.79 (3H, s), 3.81 (3H, s), 5.10 (2H, s), 5.75 (2H, s), 6.84 (1H, d), 6.85 (2H, d), 6.87 (2H, d), 7.34 (2H, d), 7.35 (2H, d), 7.64 (1H, dd), 8.27 (1H, d).

(0200)

Step 2

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-(4-methoxybenzyl) oxy phenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-6-(4-methoxybenzyl) oxy phenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-(4-methoxybenzyl) oxy phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 159-160°C (recrystallization solvent = chloroform - n-hexane). NMR (400 MHz, CDCl3) δ ppm 1.88-2.10 (2H, m), 2.26-2.41 (4H, m), 3.68 (1H, m), 3.79 (3H, s), 3.81 (3H, s), 5.17 (2H, s), 5.74 (2H, s), 6.87 (2H, d), 6.88 (2H, d), 6.92 (1H, d), 7.07 (1H, d), 7.35 (2H, d), 7.39 (2H, d), 7.62 (1H, dd), 8.23 (1H, d).

(0201)

Step 3

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-hydroxyphenyl)-1H-tetrazole.

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-(4-methoxybenzyl) oxy phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 205-209°C (decomp) (recrystallization solvent = ethanol-ether). NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.03 (2H, m), 2.18-2.33 (4H, m), 3.66 (1H, m), 7.15 (1H, d), 7.49 (1H, s), 7.70 (1H, dd), 8.44 (1H, d).

Elemental analysis value,

Theoretical value (%) of C16H13N5OS, C, 57.82, H, 4.25, N, 21.07,

Measured values (%) C, 57.43, H, 4.32, N, 20.79..

(0202)

Example 39

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-fluorophenyl)-1H-tetrazole:

Step 1

Synthesis of 5-(3-iodo-2-fluorophenyl)-1H-tetrazole.

Trifluoroacetic acid 0.32 ml was added under ice cooling with stirring to 2,6-lutidine 1.65 g. It was stirred at the same temperature for 30 minutes, thereafter, sodium azide 270 mg was added, and the mixture was stirred at room temperature for one hour. 3-iodo-2-fluorobenzo nitrile 1 g was added to this, and the mixture was stirred at 80°C for 16 hours. The reaction liquor was added to 2N hydrochloric acid 50 ml, and precipitated crystals were recovered by filtration and, after washing with water, were dried. The crude crystals were recrystallised from chloroform - ethanol, and 5-(3-iodo-2-fluorophenyl)-1H-tetrazole 1.05 g was obtained as prism crystals.
mp. 182-184°C. NMR (400 MHz, DMSO-d6) δ ppm 7.25 (1H, m), 8.16 (1H, m), 8.21 (1H, m), MS(EI)m/z 290(M+).
Elemental analysis value,
Theoretical value (%) of C7H4FIN4, C, 28.99, H, 1.39, N, 19.32,
Measured values (%) C, 29.26, H, 1.59, N, 19.05..

(0203)

Step 2

Synthesis of 5-(3-iodo-2-fluorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-2-fluorophenyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(3-iodo-2-fluorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.
mp. 124-126°C. NMR (400 MHz, DMSO-d6) δ ppm 3.75 (3H, s), 5.95 (2H, s), 6.97 (2H, d), 7.18 (1H, t), 7.40 (2H, d), 8.03 (2H, m), MS(EI)m/z 410(M+).
Elemental analysis value,
Theoretical value (%) of C15H12FIN4O, C, 43.92, H, 2.95, N, 13.66,
Measured values (%) C, 43.89, H, 3.02, N, 13.83..

(0204)

Step 3

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-fluorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-2-fluorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-fluorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.
mp. 114-116°C (recrystallization solvent = chloroform - n-hexane). NMR (400 MHz, CDCl3) δ ppm 1.92-2.40 (6H, m), 3.66-3.75 (1H, m), 3.80 (3H, s), 5.78 (2H, s), 6.89-6.93 (2H, m), 6.99 (1H, s), 7.27 (1H, t), 7.40-7.43 (2H, m), 7.65-7.69 (1H, m), 8.13-8.17 (1H, m), MS(FAB)m/z 445 (M+ +1).
Elemental analysis value,
Theoretical value (%) of C24H20FN5OS, C, 64.70, H, 4.52, N, 15.72,

Measured values (%) C, 64.73, H, 4.56, N, 15.81..

(0205)

Step 4

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-fluorophenyl)-1H-tetrazole.

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-fluorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 192-195°C (recrystallization solvent = chloroform - n-hexane).

IR v max cm-1 2224. NMR (400 MHz, CDCl3) δ ppm 1.85-2.35 (6H, m), 3.65-3.74 (1H, m), 7.55 (1H, t), 7.61 (1H, s), 7.97-8.01 (1H, m), 8.17-8.21 (1H, m),

MS(FAB)m/z 326 (M+ +1).

Elemental analysis value,

Theoretical value (%) of C16H12FN5 S, 59.06, H, 3.72, N, 21.52,

Measured values (%) C, 58.89, H, 3.79, N, 21.45..

(0206)

Example 40

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methylthio phenyl)-1H-tetrazole:

Step 1

Synthesis of 5-(3-iodo-6-methylthio phenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-2-fluorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole 204 mg was dissolved in DMSO 10 ml, and methanethiol sodium salt (about 15 % containing aqueous solution) 0.5 ml were added, and the mixture was stirred at room temperature for three hours. The reaction liquor was discharged into 1N hydrochloric acid 100 ml, and precipitated crystals were recovered by filtration and, after washing with water, were dried. The crude crystals were recrystallised from chloroform - n-hexane, and 5-(3-iodo-6-methylthio phenyl)-2-(4-methoxybenzyl)-2H-tetrazole 183 mg was obtained as needle crystals.

mp. 138-140°C. NMR (400 MHz, CDCl3) δ ppm 2.46 (3H, s), 3.80 (3H, s), 5.77 (2H, s), 6.89-6.91 (2H, m), 7.05 (1H, d), 7.69 (1H, dd), 8.29 (1H, d), MS(EI)m/z 438(M+).

Elemental analysis value,

Theoretical value (%) of C16H15IN4OS, C, 43.85, H, 3.45, N, 12.78,

Measured values (%) C, 44.17, H, 3.55, N, 12.91..

(0207)

Step 2

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methylthio phenyl)-1H-tetrazole.

5-(3-iodo-6-methylthio phenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and continuing, it was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 114-116°C (recrystallization solvent = chloroform - ethanol).
IR v max cm-1 2216. NMR (400 MHz, DMSO-d6) δ ppm 1.86-2.32 (6H, m), 2.67 (3H, s), 3.63-3.71 (1H, m), 7.53 (1H, s), 7.57 (1H, t), 7.82 (1H, dd), 7.99 (1H, d),
MS(FAB)m/z 354 (M+ +1).
Elemental analysis value,
Theoretical value (%) of C17H15N5S2, C, 57.77, H, 4.28, N, 19.81,
Measured values (%) C, 57.31, H, 4.34, N, 19.65..

(0208)

Example 41

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-chlorophenyl)-1H-tetrazole:

Step 1

Synthesis of 5-(6-chloro-3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(6-chloro-3-iodo phenyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(6-chloro-3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.
mp. 90-91°C. NMR (400 MHz, CDCl3) δ ppm 3.80 (3H, s), 5.77 (2H, s), 6.89 (2H, d), 7.23 (1H, d), 7.39 (2H, d), 7.68 (1H, d), 8.25 (1H, d).

(0209)

Step 2

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-chlorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(6-chloro-3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-chlorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.
mp. 66-67°C (recrystallization solvent = ether-n-hexane). NMR (400 MHz, CDCl3) δ ppm 1.88-2.11 (2H, m), 2.26-2.42 (4H, m), 3.69 (1H, m), 3.81 (3H, s), 5.79 (2H, s), 6.91 (2H, d), 6.97 (1H, s), 7.41 (2H, d), 7.51 (1H, d), 7.58 (1H, dd), 8.17 (1H, d).

(0210)

Step 3

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-chlorophenyl)-1H-tetrazole.

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-chlorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 183-185°C (recrystallization solvent = ethanol-ether). NMR (400 MHz, DMSO-d6) δ ppm 1.86-2.02 (2H, m), 2.18-2.31 (4H, m), 3.68 (1H, m), 7.57 (1H, s), 7.83 (1H, d), 7.90 (1H, d), 8.13 (1H, s), MS(EI)m/z 341(M+).
Elemental analysis value,
Theoretical value (%) of C16H12N5ClS, C, 56.22, H, 3.54, N, 20.49,
Measured values (%) C, 56.02, H, 3.63, N, 20.21..

(0211)

Example 42

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-chlorophenyl)-1H-tetrazole:

Step 1

Synthesis of 5-(2-chloro-3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(2-chloro-3-iodo phenyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(2-chloro-3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.
mp. 91-92°C. NMR (400 MHz, CDCl3) δ ppm 3.76 (3H, s), 5.78 (2H, s), 6.90 (2H, d), 7.06 (1H, t), 7.40 (2H, d), 7.82 (1H, d), 7.99 (1H, d).

(0212)

Step 2

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-chlorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(2-chloro-3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-chlorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.
mp. 69-70°C (recrystallization solvent = ether-n-hexane). NMR (400 MHz, CDCl3) δ ppm 1.89-2.11 (2H, m), 2.26-2.40 (4H, m), 3.72 (1H, m), 3.80 (3H, s), 5.79 (2H, s), 6.91 (2H, d), 7.00 (1H, s), 7.34 (1H, t), 7.41 (2H, d), 7.72 (1H, d), 7.97 (1H, d).

(0213)

Step 3

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-chlorophenyl)-1H-tetrazole.

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-chlorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 167-170°C (recrystallization solvent = water - ethanol).

IR v max cm-1 2220. NMR (400 MHz, DMSO-d6) δ ppm 1.83-2.10 (2H, m), 2.19-2.35 (4H, m), 3.70 (1H, m), 7.61 (1H, s), 7.65 (1H, t), 7.92 (1H, dd), 8.02 (1H, dd), MS(EI)m/z 341(M+).
Elemental analysis value,
Theoretical value (%) of C16H12N5ClS, C, 56.22, H, 3.54, N, 20.49,
Measured values (%) C, 56.35, H, 3.76, N, 19.94..

(0214)

Example 43.

5-(3-[2-(4-isopropyl-2-thiazolyl) ethinyl)-2-fluorophenyl)-1H-tetrazole.

Step 1.

Synthesis of 5-(3-(2-(4-isopropyl-2-thiazolyl) ethinyl)-2-fluorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-2-fluorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-isopropyl-2-ethinyl thiazole synthesised in Example 39 were treated in the same way as in Step 4 of Example 1, and 5-(3-(2-(4-isopropyl-2-thiazolyl) ethinyl)-2-fluorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.
mp. 116-119°C. NMR (400 MHz, CDCl3) δ ppm 1.35 (6H, d), 3.12-3.19 (1H, m), 3.80 (3H, s), 5.78 (2H, s), 6.89-6.92 (2H, d), 6.98 (1H, s), 7.27 (1H, t), 7.39-7.41 (2H, d), 7.64-7.68 (1H, m), 8.12-8.17 (1H, m), MS(EI)m/z 433(M+).
Elemental analysis value,
Theoretical value (%) of C23H20FN5OS, C, 63.73, H, 4.65, N, 16.16,
Measured values (%) C, 63.69, H, 4.69, N, 16.22..

(0215)

Step 2

Synthesis of 5-(3-(2-(4-isopropyl-2-thiazolyl) ethinyl)-2-fluorophenyl)-1H-tetrazole.

5-(3-iodo-2-fluorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-isopropyl-2-ethinyl thiazole were treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 155-158°C (recrystallization solvent = chloroform - n-hexane),
IR v max cm-1 2220. NMR (400 MHz, DMSO-d6) δ ppm 1.28 (6H, d), 3.07-3.16 (1H, m), 7.55 (1H, t), 7.58 (1H, s), 7.97-8.00 (1H, m), 8.17-8.20 (1H, m), MS(EI)m/z 313(M+).
Elemental analysis value,
Theoretical value (%) of C15H12FN5S, C, 57.49, H, 3.86, N, 22.35,
Measured values (%) C, 57.50, H, 3.95, N, 22.29..

(0216)

Example 44

5-(3-(2-(4-n-propyl-2-thiazolyl) ethinyl)-2-fluorophenyl)-1H-tetrazole:

Step 1

Synthesis of 5-(3-(2-(4-n-propyl-2-thiazolyl) ethinyl)-2-fluorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-2-fluorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-n-propyl-2-ethinyl thiazole used in an example 39 were treated in the same way as in Step 4 of Example 1, and 5-(3-(2-(4-n-propyl-2-thiazolyl) ethinyl)-2-fluorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.
mp. 97-99°C. NMR (400 MHz, CDCl3) δ ppm 0.98 (3H, t), 1.78 (2H, m), 2.80 (2H, t), 3.80 (3H, s), 5.78 (2H, s), 6.89-6.91 (2H, d), 6.98 (1H, s), 7.27 (1H, t), 7.40-7.42 (2H, d), 7.64-7.68 (1H, m), 8.12-8.16 (1H, m), MS(EI)m/z 433(M+).
Elemental analysis value,
Theoretical value (%) of C23H20FN5OS, C, 63.73, H, 4.65,N, 16.16,
Measured values (%) C, 63.58, H, 4.71, N, 16.02..

(0217)

Step 2

Synthesis of 5-(3-(2-(4-n-propyl-2-thiazolyl) ethinyl)-2-fluorophenyl)-1H-tetrazole.

5-(3-(2-(4-n-propyl-2-thiazolyl) ethinyl)-2-fluorophenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 149-152°C (recrystallization solvent = chloroform - n-hexane).
IR v max cm-1 2224. NMR (400 MHz, DMSO-d6) δ ppm 0.92 (3H, t), 1.70 (2H, m), 2.75 (2H, t), 7.55 (1H, t), 7.59 (1H, s), 7.94-8.01 (1H, m), 8.14-8.22 (1H, m), MS(EI)m/z 313(M+).
Elemental analysis value,
Theoretical value (%) of C15H12FN5S, C, 57.49, H, 3.86, N, 22.35,
Measured values (%) C, 57.47, H, 3.98, N, 22.11..

(0218)

Example 45

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylphenyl)-1H-tetrazole:

Step 1

Synthesis of 5-(3-iodo-2-methylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-2-methylphenyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(3-iodo-2-methylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as an oily substance.

NMR (400 MHz, CDCl3) δ ppm 2.76 (3H, s), 3.80 (3H, s), 5.75 (2H, s), 6.90 (2H, d), 7.39 (2H, d), 7.81 (1H, dd), 7.94 (1H, dd).

(0219)

Step 2

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-2-methylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 140-142°C (recrystallization solvent = ether-n-hexane). NMR (400 MHz, CDCl3) δ ppm 1.88-2.11 (2H, m), 2.27-2.42 (4H, m), 2.77 (3H, s), 3.69 (1H, m), 3.81 (3H, s), 5.77 (2H, s), 6.91 (2H, d), 6.97 (1H, s), 7.30 (1H, t), 7.41 (2H, d), 7.67 (1H, dd), 7.96 (1H, dd).

Elemental analysis value,

Theoretical value (%) of C25H23N5OS, C, 68.00, H, 5.25, N, 15.86,

Measured values (%) C, 67.83, H, 5.26, N, 15.94..

(0220)

Step 3

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylphenyl)-1H-tetrazole.

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 209-211°C (recrystallization solvent = ethanol-ether). NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.06 (2H, m), 2.19-2.34 (4H, m), 2.64 (3H, s), 3.69 (1H, m), 7.52 (1H, t), 7.56 (1H, s), 7.79 (1H, d), 7.85 (1H, d), MS(EI)m/z 321(M+).

Elemental analysis value,

Theoretical value (%) of C17H15N5S, C, 63.53,H, 4.70, N, 21.79,

Measured values (%) C, 63.44, H, 4.80, N, 21.73..

(0221)

Example 46

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-trifluoromethylphenyl)-1H-tetrazole:

Step 1

Synthesis of 5-(3-iodo-2-trifluoromethylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-2-trifluoromethylphenyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(3-iodo-2-trifluoromethylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as an oily substance.
NMR (400 MHz, CDCl3) δ ppm 3.81 (3H, s), 5.76 (2H, s), 6.91 (2H, d), 7.22 (1H, t), 7.36 (2H, d), 7.48 (1H, d), 8.22 (1H, d).

(0222)

Step 2

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-trifluoromethylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-trifluoromethylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-trifluoromethylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as an oily substance.
NMR (400 MHz, CDCl3) δ ppm 1.90-2.11 (2H, m), 2.26-2.43 (4H, m), 3.63-3.77 (1H, m), 3.81 (3H, s), 5.78 (2H, s), 6.91 (2H, d), 7.02 (1H, s), 7.38 (2H, d), 7.57-7.63 (1H, m), 7.88-7.90 (1H, m).

(0223)

Step 3

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-trifluoromethylphenyl)-1H-tetrazole.

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-trifluoromethylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 209-211°C (recrystallization solvent = chloroform - n-hexane).
IR v max cm-1 2224. NMR (400 MHz, DMSO-d6) δ ppm 1.89-2.04 (2H, m), 2.21-2.35 (1H, m), 3.70 (1H, m), 7.63 (1H, s), 7.80 (1H, d), 7.94 (1H, t), 8.19 (1H, d),
MS(FAB)m/z 376 (M+ +1).
Elemental analysis value,
Theoretical value (%) of C17H12F3N5S • 1/2 H2O, C, 53.12, H, 3.41, N, 18.22,
Measured values (%) C, 53.39, H, 3.27, N, 18.44..

(0224)

Example 47

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-trifluoromethylphenyl)-1H-tetrazole:

Step 1

Synthesis of 5-(3-iodo-6-trifluoromethylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-6-trifluoromethylphenyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(3-iodo-6-trifluoromethylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 59-61°C. NMR (400 MHz, CDCl3) δ ppm 3.81 (3H, s), 5.77 (2H, s), 6.91 (2H, d), 7.38 (2H, d), 7.52 (1H, d), 7.94 (1H, dd), 8.22 (1H, d).

(0225)

Step 2

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-trifluoromethylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-trifluoromethylphenyl)-1H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-trifluoromethylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as an oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.89-2.17 (2H, m), 2.27-2.41 (4H, m), 3.70 (1H, m), 3.81 (3H, s), 5.78 (2H, s), 6.92 (2H, d), 7.00 (1H, s), 7.39 (2H, d), 7.78 (1H, d), 7.83 (1H, d), 8.08 (1H, s).

(0226)

Step 3

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-trifluoromethylphenyl)-1H-tetrazole.

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-trifluoromethylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 209-211°C (recrystallization solvent = chloroform - ethanol-n-hexane).

IR v max cm-1 2224. NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.06 (2H, m), 2.19-2.34 (1H, m), 3.69 (1H, m), 7.61 (1H, s), 8.03-8.13 (1H, m), 8.16 (1H, s),

MS(FAB)m/z 376 (M+ +1).

Elemental analysis value,

Theoretical value (%) of C17H12F3N5S, C, 54.40, H, 3.22, N, 18.66,

Measured values (%) C, 54.29, H, 3.38, N, 18.41..

(0227)

Example 48

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-5-carbomethoxyphenyl)-1H-tetrazole:

Step 1

Synthesis of 5-(3-iodo-5-carbomethoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-5-carbomethoxyphenyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(3-iodo-5-carbomethoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 97°C.

IR v max cm-1 1728. NMR (400 MHz, CDCl3) δ ppm 3.80 (3H, s), 3.95 (3H, s), 5.75 (2H, s), 6.91 (2H, d), 7.39 (2H, d), 8.44 (1H, s), 8.66 (1H, d), 8.74 (4H, s), MS(EI)m/z 450(M+).

Elemental analysis value,

Theoretical value (%) of C17H15IN4O3, C, 46.35, H, 3.36, N, 12.44,

Measured values (%) C, 46.08, H, 3.65, N, 12.50..

(0228)

Step 2

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-5-carbomethoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-5-carbomethoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-5-carbomethoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as a brown oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.93-2.40 (6H, m), 3.71 (1H, m), 3.81 (3H, s), 3.97 (3H, s), 5.75 (2H, s), 6.92 (2H, d), 6.99 (1H, s), 7.41 (2H, d), 8.32 (1H, d), 8.54 (1H, t), 8.79 (1H, d).

(0229)

Step 3

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-5-carbomethoxyphenyl)-1H-tetrazole.

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-5-carbomethoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 189-191°C (recrystallization solvent = methylene chloride).

IR v max cm-1 2224, 1720. NMR (400 MHz, DMSO-d6) δ ppm 1.80-2.32 (6H, m), 3.69 (1H, m), 3.98 (3H, s), 7.60 (1H, s), 8.32 (1H, s), 8.53 (1H, s), 8.68 (1H, s),

MS(FAB)m/z 366 (M+ +1).

Elemental analysis value,

Theoretical value (%) of C18H15N5O2S, C, 59.16, H, 4.14, N, 19.17,

Measured values (%) C, 58.79, H, 4.14, N, 18.76..

(0230)

Example 49

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methoxyphenyl)-1H-tetrazole:

Step 1

Synthesis of 5-(3-iodo-6-methoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-6-methoxyphenyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(3-iodo-6-methoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 133-135°C (recrystallization solvent = chloroform - n-hexane). NMR (400 MHz, CDCl3) δ ppm 3.80 (3H, s), 5.76 (2H, s), 6.80 (1H, d), 6.89-6.91 (2H, m), 7.37-7.39 (1H, m), 7.70 (1H, dd), 8.20 (1H, d), MS(EI)m/z 422(M+).

Elemental analysis value,

Theoretical value (%) of C16H15IN4O2, C, 45.52, H, 3.58,N, 13.27,

Measured values (%) C, 45.49, H, 3.68, N, 13.29..

(0231)

Step 2

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-6-methoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 98-101°C. NMR (400 MHz, CDCl3) δ ppm 1.93-2.40 (6H, m), 3.71 (1H, m), 3.64-3.73 (1H, m), 3.80 (3H, s), 3.96 (3H, s), 5.77 (2H, s), 6.89-6.92 (2H, m), 6.93 (1H, s), 7.03 (1H, d), 7.38-7.42 (2H, m), 7.66 (1H, dd), 8.17 (1H, d), MS(EI)m/z 457(M+).

Elemental analysis value,

Theoretical value (%) of C25H23N5O2S, C, 65.63, H, 5.07, N, 15.31,

Measured values (%) C, 65.40, H, 5.03, N, 15.45..

(0232)

Step 3

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methoxyphenyl)-1H-tetrazole.

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 219-221°C (recrystallization solvent = chloroform - n-hexane),

IR v max cm-1 2216. NMR (400 MHz, DMSO-d6) δ ppm 1.86-2.34 (6H, m), 3.63-3.71 (1H, m), 4.04 (3H, s), 7.39 (1H, d), 7.51 (1H, s), 7.88 (1H, dd), 8.29 (1H, d), MS(EI)m/z 337(M+).

Elemental analysis value,

Theoretical value (%) of C17H15N5OS, C, 60.52, H, 4.48, N, 20.76,
Measured values (%) C, 60.50, H, 4.60, N, 20.93..

(0233)

Example 50

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylthio phenyl)-1H-tetrazole:

Step 1

Synthesis of 5-(3-iodo-2-methylthio phenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-2-methylthio phenyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(3-iodo-2-methylthio phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as a straw-coloured oily substance.

NMR (400 MHz, CDCl3) δ ppm 2.30 (3H, s), 3.80 (3H, s), 5.77 (2H, s), 6.88-6.92 (2H, m), 7.07 (1H, t), 7.38-7.41 (2H, m), 7.61 (1H, dd), 8.06 (1H, dd).

(0234)

Step 2

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylthio phenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-2-methylthio phenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylthio phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as brown oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.89-2.40 (6H, m), 2.44 (3H, s), 3.67-3.75 (1H, m), 3.80 (3H, s), 5.79 (2H, s), 6.89-6.91 (2H, m), 6.99 (1H, s), 7.36 (1H, d), 7.40-7.42 (2H, m), 7.69 (1H, dd), 7.73 (1H, dd).

(0235)

Step 3

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylthio phenyl)-1H-tetrazole.

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylthio phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 151-154°C (recrystallization solvent = chloroform - n-hexane),

IR v max cm-1 2212. NMR (400 MHz, DMSO-d6) δ ppm 1.86-2.32 (6H, m), 2.39 (3H, s), 3.65-3.73 (1H, m), 7.59 (1H, s), 7.62 (1H, t), 7.72 (1H, d), 7.95 (1H, d), MS(EI)m/z 353(M+).

Elemental analysis value,

Theoretical value (%) of C17H15N5S2, C, 57.77, H, 4.28, N, 19.81,
Measured values (%) C, 57.64, H, 4.38, N, 19.60..

(0236)

Example 51

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-5-bromo phenyl)-1H-tetrazole:

Step 1

Synthesis of 5-(3-iodo-5-bromo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-5-bromo phenyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(3-iodo-5-bromo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.
mp. 154-155°C (recrystallization solvent = chloroform - n-hexane). NMR (400 MHz, CDCl3) δ ppm 3.80 (3H, s), 5.72 (2H, s), 6.90 (2H, d), 7.37 (2H, d), 7.92 (1H, t), 8.24 (1H, t), 8.40 (1H, t), MS(FAB)m/z 473 (M+ +1).
Elemental analysis value,
Theoretical value (%) of C15H12BrIN4O, C, 38.24, H, 2.57, N, 11.90,
Measured values (%) C, 38.25, H, 2.54, N, 12.10..

(0237)

Step 2

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-5-bromo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-5-bromo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-5-bromo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.
mp. 127-129°C (recrystallization solvent = chloroform - n-hexane). NMR (400 MHz, CDCl3) δ ppm 1.95-2.09 (2H, m), 2.29-2.40 (4H, m), 3.68-3.72 (1H, m), 3.80 (3H, s), 5.73 (2H, s), 6.91 (2H, d), 6.99 (1H, s), 7.40 (1H, d), 7.78 (1H, t), 8.29-8.39 (1H, m),
MS(FAB)m/z 508 [(M+ +2) +1)], 506 [(M+) +1))].
Elemental analysis value,
Theoretical value (%) of C24H20BrN5OS • 1/4 H2O, C, 56.42, H, 4.04, N, 13.71,
Measured values (%) C, 56.49, H, 4.07, N, 13.69..

(0238)

Step 3

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-5-bromo phenyl)-1H-tetrazole.

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-5-bromo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 104-105°C (decomp) (recrystallization solvent = chloroform - ethanol-n-hexane).
IR v max cm-1 2210. NMR (400 MHz, DMSO-d6) δ ppm 2.06 (2H, m), 2.19-2.32 (4H, m), 3.73 (1H, m), 7.59 (1H, s), 8.14 (1H, s), 8.28 (1H, s), 8.30 (1H, s),
MS(FAB)m/z 388 [(M+ +2) +1)], 386 [(M+) +1)].
Elemental analysis value,
Theoretical value (%) of C16H12BrN5S • 1/4 H2O, C, 49.18, H, 3.22, N, 17.92,
Measured values (%) C, 49.20, H, 3.12, N, 17.88..

(0239)

Example 52

5-(3,5-bis [2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole:

Step 1

Synthesis of 5-(3,5-diiodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-bromo-5-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 2 of Example 16, and 5-(3,5-diiodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.
mp. 177-178°C (recrystallization solvent = chloroform - n-hexane). NMR (400 MHz, CDCl3) δ ppm 3.80 (3H, s), 5.72 (2H, s), 6.91 (2H, d), 7.37 (2H, d), 8.11-8.12 (1H, m), 8.43 (2H, d).

(0240)

Step 2

Synthesis of 5-(3,5-bis [2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3,5-diiodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(3,5-bis [2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as dark brown amorphous material.
NMR (400 MHz, CDCl3) δ ppm 1.90-2.11 (4H, m), 2.28-2.42 (8H, m), 3.66-3.75 (1H, m), 3.80 (3H, s), 5.74 (2H, s), 6.92 (2H, d), 6.98 (2H, s), 7.41 (2H, d), 7.82 (1H, s), 8.37 (2H, d).

(0241)

Step 3

Synthesis of 5-(3,5-bis [2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole.

5-(3,5-bis [2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 212-214°C (decomp) (recrystallization solvent = chloroform - ethanol - n-hexane).
IR v max cm-1 2216. NMR (400 MHz, DMSO-d6) δ ppm 1.85-2.06 (4H, m), 2.19-2.34 (8H, m), 3.65-3.73 (2H, m), 7.59 (1H, s), 8.16 (1H, s), 8.36 (2H, d),
MS(FAB)m/z 469 (M+ +1).
Elemental analysis value,
Theoretical value (%) of C25H20N6S2 • 3/4 H2O, C, 62.28, H, 4.49, N, 17.43,
Measured values (%) C, 62.46, H, 4.38, N, 17.49..

(0242)

Example 53

5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-3-(1H-tetrazol-5-yl) phenyl)-1H-tetrazole:

Step 1

Synthesis of 5-(5-iodo-3-(-2-(4-methoxybenzyl)-2H-tetrazol-5-yl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(5-iodo-3-(-2-(4-methoxybenzyl)-2H-tetrazol-5-yl) phenyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(5-iodo-3-(-2-(4-methoxybenzyl)-2H-tetrazol-5-yl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.
mp. 183-186°C (recrystallization solvent = chloroform - n-hexane). NMR (400 MHz, CDCl3) δ ppm 3.80 (6H, s), 5.74 (4H, s), 6.91 (4H, d), 7.39 (4H, d), 8.56 (2H, d), 8.82-8.83 (1H, m).

(0243)

Step 2

Synthesis of 5-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-3-(1H-tetrazol-5-yl) phenyl)-1H-tetrazole.

5-(5-iodo-3-(-2-(4-methoxybenzyl)-2H-tetrazol-5-yl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and continuing, this was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. >300°C (recrystallization solvent = chloroform - ethanol-n-hexane),
IR v max cm-1 2220. NMR (400 MHz, DMSO-d6) δ ppm 1.88-2.04 (2H, m), 2.23-2.35 (4H, m), 3.66-3.74 (1H, m), 7.61 (1H, s), 8.46 (2H, d), 8.86-8.87 (1H, m).
Elemental analysis value,
Theoretical value (%) of C17H13N9S • 1/2 H2O, C, 53.12, H, 3.67, N, 32.79,
Measured values (%) C, 53.25, H, 4.05, N, 33.06..

(0244)

Example 54

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methoxyphenyl)-1H-tetrazole:

Step 1

Synthesis of 5-(3-iodo-2-methoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-2-methoxyphenyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(3-iodo-2-methoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 65-69°C (recrystallization solvent = chloroform - n-hexane). NMR (400 MHz, CDCl3) δ ppm 3.78 (3H, s), 3.80 (3H, s), 5.77 (2H, s), 6.88-6.91 (2H, m), 6.97 (1H, t), 7.39-7.41 (2H, m), 7.90 (1H, dd), 8.02 (1H, dd), MS(EI)m/z 422(M+).

Elemental analysis value,

Theoretical value (%) of C16H15IN4O2, C, 45.52, H, 3.58, N, 13.27,

Measured values (%) C, 45.69, H, 3.75, N, 13.48..

(0245)

Step 2

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methoxyphenyl)-1H-tetrazole.

5-(3-iodo-2-methoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and continuing, this was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 153-155°C (recrystallization solvent = chloroform - n-hexane).

IR v max cm-1 2216. NMR (400 MHz, DMSO-d6) δ ppm 1.85-2.34 (6H, m), 3.65-3.73 (1H, m), 4.01 (3H, s), 7.42 (1H, t), 7.59 (1H, s), 7.88 (1H, dd), 8.12 (1H, dd), MS(EI)m/z 337(M+).

Elemental analysis value,

Theoretical value (%) of C17H15N5OS, C, 60.52, H, 4.48, N, 20.76,

Measured values (%) C, 60.34, H, 4.53, N, 20.60..

(0246)

Example 55

Ethyl 4-(2-(4-cyclobutyl-2-thiazolyl) ethinyl-2-(1H-tetrazol-5-yl) phenoxy acetate.

Step 1.

Synthesis of ethyl 4-(2-iodo-2-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl) phenoxy acetate and ethyl 4-(2-iodo-2-(2-(4-methoxy-5-yl)-2H-tetrazol-5-yl) phenoxy acetate.

4-(2-iodo-2-(1H-tetrazol-5-yl) phenoxy acetate was treated in the same way as in Step 3 of Example 1. 4-(2-iodo-2-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl) phenoxy acetate and ethyl 4-(2-iodo-2-(2-(4-methoxy-5-yl)-2H-tetrazol-5-yl) phenoxy acetate were obtained as about 1= 1 mixture.

NMR (400 MHz, CDCl3) δ ppm 1.26 and 1.29 (3H, each t), 3.76 and 3.79 (3H, each s), 4.23 and 4.25 (2H, each q), 4.59 and 4.70 (2H, s), 5.58 and 5.75 (2H, each s), 6.63 and 6.72 (1H, each d), 6.74-6.76 and 6.88-6.90 (2H, each m), 6.98-7.00 and 7.38-7.41' 2H, each m), 7.52 (1/2 H, d), 7.67 and 7.76 (1H, each dd), 8.27 (1/2 H, d).

(0247)

Step 2

Synthesis of ethyl 4-(2-(4-cyclobutyl-2-thiazolyl) ethinyl-2-(1H-tetrazol-5-yl) phenoxy acetate.

Ethyl 4-(2-iodo-2-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl) phenoxy acetate and ethyl 4-(2-iodo-2-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) phenoxy acetate mixture (1 : 1) and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and continuing, this was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 176-178°C (recrystallization solvent = chloroform - n-hexane).

IR v max cm-1 2216, 1730. NMR (400 MHz, DMSO-d6) δ ppm 1.26 (3H, t), 1.84-2.33 (6H, m), 3.63-3.71 (1H, m), 4.17 (2H, q), 5.13 (2H, s), 7.34 (1H, d), 7.52 (1H, s), 7.83 (1H, d), 8.31 (1H, s), MS(EI)m/z 409(M+).

Elemental analysis value,

Theoretical value (%) of C20H19N5O3S, C, 58.67, H, 4.68, N, 17.10,

Measured values (%) C, 58.67, H, 4.68, N, 17.16..

(0248)

Example 56

4-(2-(4-cyclobutyl-2-thiazolyl) ethinyl-2-(1H-tetrazol-5-yl) phenoxyacetic acid :

THF 5ml and 0.25N sodium hydroxide aqueous solution 10 ml were added to ethyl 4-(2-(4-cyclobutyl-2-thiazolyl) ethinyl-2-(1H-tetrazol-5-yl) phenoxy acetate 350 mg, and the mixture was stirred at room temperature for one hour. The reaction liquor was discharged into water 100 ml, and 1N hydrochloric acid 10 ml was added. The precipitated crystals were recovered by filtration, and it was dried after washing with water. The crude crystals were recrystallised from chloroform - ethanol, and the title substance 290 mg was obtained as a crystalline powder.

mp. 251-255°C.

IR v max cm-1 2216, 1720. NMR (400 MHz, DMSO-d6) δ ppm 1.86-2.34 (6H, m), 3.63-3.71 (1H, m), 5.06 (2H, s), 7.34 (1H, d), 7.52 (1H, s), 7.85 (1H, dd), 8.34 (1H, d), MS(EI)m/z 381(M+).

Elemental analysis value,
Theoretical value (%) of C18H15N5O3S, C, 56.68, H, 3.96,N, 18.36,
Measured values (%) C, 56.54, H, 4.10, N, 18.14..

(0249)

Example 57

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-hydroxyphenyl)-1H-tetrazole:

Step 1

Synthesis of 5-(2-hydroxy-3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

Using 2 equivalents of 4-methoxybenzyl chloride and potassium carbonate, 5-(2-hydroxy-3-iodo phenyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(2-hydroxy-3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as an oily substance.
NMR (400 MHz, CDCl3) δ ppm 3.78 (3H, s), 3.82 (3H, s), 4.89 (2H, s), 5.73 (2H, s), 6.84-6.88 (4H, m), 6.99 (1H, t), 7.32-7.34 (2H, m), 7.37-7.40 (2H, m), 7.94 (1H, dd), 8.04 (1H, dd).

(0250)

Step 2

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-hydroxyphenyl)-1H-tetrazole.

5-(2-hydroxy-3-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and continuing, this was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 195-199°C (decomp) (recrystallization solvent = chloroform) IR v max cm-1 3116, 2980, 2948, 2216, 1616, 1588, 1554, 1512. NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.34 (6H, m), 3.63-3.72 (1H, m), 7.16 (1H, t), 7.52 (1H, s), 7.75 (1H, dd), 8.04 (1H, dd), MS(EI)m/z 323(M+).
Elemental analysis value,
Theoretical value (%) of C16H13N5OS, C, 58.61, H, 4.15, N, 21.36,
Measured values (%) C, 58.69, H, 4.13,N, 21.04..

(0251)

Example 58

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-isopropoxy phenyl)-1H-tetrazole:

Step 1

Synthesis of 5-(3-iodo-2-isopropoxy phenyl)-1-(4-methoxybenzyl)-1H-tetrazole.

5-(3-iodo-2-isopropoxy phenyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(3-iodo-2-isopropoxy phenyl)-1-(4-methoxybenzyl)-1H-tetrazole was obtained as an oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.05 (6H, d), 3.71 (3H, s), 4.05-4.06 (1H, m), 5.51 (2H, s), 6.68-6.71 (2H, m), 6.89-6.92 (2H, m), 6.91 (1H, t), 7.29 (1H, dd), 7.99 (1H, dd).

(0252)

Step 2

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-isopropoxy phenyl)-1H-tetrazole.

5-(3-iodo-2-isopropoxy phenyl)-1-(4-methoxybenzyl)-1H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and continuing, this was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 193-196°C (decomp) (recrystallization solvent = chloroform - n-hexane).

IR v max cm-1 3096, 2976, 2216, 1600,

NMR (400 MHz, CDCl3) δ ppm 1.33 (6H, d), 1.92-2.45 (6H, m), 3.72-3.80 (1H, m), 5.10-5.18 (1H, m), 7.04 (1H, s), 7.28 (1H, t), 7.66 (1H, d), 8.37 (1H, d), 13.30 (1H, br s), MS(EI)m/z 365(M+).

Elemental analysis value,

Theoretical value (%) of C19H19N5OS, C, 62.44, H, 5.24,N, 19.16,

Measured values (%) C, 62.45, H, 5.27, N, 19.29..

(0253)

Example 59

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl] ethinyl)-6-methylphenyl)-1H-tetrazole

Step 1

5-(3-iodo-6-methylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-6-methylphenyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(3-iodo-6-methylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 67-69°C (recrystallization solvent : ethanol-water).

NMR (400 MHz, CDCl3) δ ppm 1.33 (6H, d), 2.56 (3H, s), 3.81 (3H, s), 5.75 (2H, s), 6.21 (2H, d), 7.04 (1H, d), 7.39 (2H, d), 7.65 (1H, dd), 8.33 (1H, d).

(0254)

Step 2

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo-6-methylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as a yellow oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.90-2.00 (1H, m), 2.00-2.10 (1H, m), 2.30-2.50 (4H, m), 2.65 (3H, s), 3.60-3.80 (1H, m), 3.81 (3H, s), 5.76 (2H, s), 6.92 (1H, s), 6.93 (2H, d), 7.31 (1H, d), 7.42 (2H, dd), 7.55 (1H, dd), 8.25 (1H, d).

(0255)

Step 3

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methylphenyl)-1H-tetrazole.

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 131-132°C (decomp) (recrystallization solvent : chloroform); IR v max cm-1 1662, 1586, 1390, 1286, 994.

NMR (400 MHz, DMSO-d6) δ ppm 1.80-2.00 (1H, m), 2.00-2.10 (1H, m), 2.20-2.40 (4H, m), 2.56 (3H, s), 3.60-3.70 (1H, m), 7.54 (1H, s), 7.56 (1H, d), 7.76 (1H, dd), 8.02 (1H, br), 8.12 (1H, s),

MS(FAB)m/z 322 (M+ +1),

Elemental analysis value of C17H15N5 S•H2O;

Theoretical value (%) C, 52.38, H, 3.97, N, 15.42.

Measured value (%) C, 52.42, H, 4.04, N, 15.51.

(0256)

Example 60

5-(2-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole

Step 1

Synthesis of 5-(2-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(2-iodo phenyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(2-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as an oily substance.

NMR (400 MHz, CDCl3) δ ppm 3.80 (3H, s), 5.77 (2H, s), 6.88-6.92 (2H, d), 7.11-7.15 (1H, m), 7.40-7.45 (3H, m), 7.71-7.73 (1H, m), 8.00-8.02 (1H, m).

(0257)

Step 2

Synthesis of 5-(2-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(2-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(2-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as brown oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.91-2.08 (2H, m), 2.30-2.39 (4H, m), 3.68-3.73 (1H, m), 3.77 (3H, s), 5.79 (2H, s), 6.81-6.84 (2H, m), 6.96 (1H, s), 7.41-7.43 (2H, m), 7.43-7.52 (2H, m), 7.72-7.75 (1H, m), 8.13-8.15 (1H, m).

(0258)

Step 3

Synthesis of 5-(2-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole.

5-(2-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 146-147°C (decomp) (recrystallization solvent : chloroform-n-hexane).

IR v max cm-1 2216.

NMR (400 MHz, DMSO-d6) δ ppm 1.82-2.04 (2H, m), 2.18-2.46 (4H, m), 3.61-3.70 (1H, m), 7.53 (1H, s), 7.67-7.73 (2H, m), 7.88-7.91 (2H, m),

MS(FAB)m/z 308 (M+ +1).

Elemental analysis value of C16H13N5S;

Theoretical value (%) C 62.51, H, 4.26, N, 22.79,

Measured value (%) C, 62.09, H, 4.28, N, 22.56..

(0259)

Example 61

5-(4-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole

Step 1

Synthesis of 5-(4-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(4-iodo phenyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(4-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as an oily substance.

mp. 122-123°C (recrystallization solvent : chloroform-n-hexane).

NMR (400 MHz, CDCl3) δ ppm 3.79 (3H, s), 5.72 (2H, s), 6.88-6.91 (2H, d), 7.36-7.39 (3H, m), 7.79-7.86 (4H, m),

MS(FAB)m/z 393 (M+ +1).

Elemental analysis value of C15H13IN4S;

Theoretical value (%) C 45.93, H, 3.34, N, 14.29.

Measured values (%) C, 46.13, H, 3.35, N, 14.47.

(0260)

Step 2

Synthesis of 5-(4-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(4-iodo phenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(4-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as brown oily substance.

mp. 140-141°C (recrystallization solvent : chloroform-n-hexane).

NMR (400 MHz, CDCl3) δ ppm 1.91-2.08 (2H, m), 2.29-2.39 (4H, m), 3.65-3.74 (1H, m), 3.97 (3H, s), 5.73 (2H, s), 6.90 (2H, d), 6.96 (1H, s), 7.38 (2H, d), 7.67 (2H, d), 8.14 (2H, m),

MS(FAB)m/z 428 (M+ +1).

Elemental analysis value of C24H21N5OS;

Theoretical value (%) C, 67.43, H, 4.95, N, 16.38.

Measured values (%) C, 67.15, H, 4.99, N, 16.12.

(0261)

Step 3

Synthesis of 5-(4-(4-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole.

5-(4-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 166-167°C (decomp) (recrystallization solvent : chloroform-n-hexane).

IR v max cm-1 2208.

NMR (400 MHz, DMSO-d6) δ ppm 1.86-2.03 (2H, m), 2.21-2.33 (4H, m), 3.63-3.72 (1H, m), 7.56 (1H, s), 7.89 (2H, d), 8.12 (2H, d),

MS(FAB)m/z 308 (M+ +1).

Elemental analysis value of C16H13N5S;

Theoretical value (%) C, 62.51, H, 4.26, N, 22.79.

Measured values (%) C, 62.31, H, 4.28, N, 22.60.

(0262)

Example 62

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-(N-methyl-N-trifluoroacetyl) aminophenyl)-1H-tetrazole

Step 1

Synthesis of 5-(3-iodo-6-(N-methyl-N-trifluoroacetyl) amino) benzonitrile.

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-(N-methyl-N-trifluoroacetyl) amino) benzonitrile and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(3-iodo-6-(N-methyl-N-trifluoroacetyl) amino) benzonitrile was obtained.

mp. 94-96°C (recrystallization solvent : chloroform-n-hexane).

NMR (400 MHz, CDCl3) δ ppm 1.85-2.45 (6H, m), 3.44 (3H, s), 3.72 (1H, m), 7.05 (1H, s), 7.42 (1H, d), 7.87 (1H, d), 7.97 (1H, s),

MS(FAB)m/z 390 (M+ +1).

Elemental analysis value of C19H14F3N3OS;

Theoretical value (%), C, 58.60, H, 3.62, N, 10.79.

Measured values (%) C, 58.18, H, 3.87, N, 10.57.

(0263)

Step 2

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-(N-methyl-N-trifluoroacetyl) aminophenyl)-1H-tetrazole.

Trifluoroacetic acid 0.095 ml was added to 2, 6-lutidine 396 mg and DMF 3 ml with stirring under ice cooling. This was stirred at room temperature for 30 minutes and thereafter, sodium azide 80 mg was added and stirred at room temperature for one hour. 5-(3-iodo-6-(N-methyl-N-trifluoroacetyl) amino) benzonitrile 320 mg was added to the reaction liquor, and the mixture was stirred at 70-75°C for six hours. After cooling, the reaction liquor was poured into 2N hydrochloric acid 50 ml. The precipitated crystals were recovered by filtration, and it washed with water and thereafter, was dried. The crude crystals were recrystallised from ether-n-hexane, and the title substance 270 mg was obtained as needle crystals.

mp. 155-156°C.

IR v max cm-1 2244, 1728, 1714. NMR (400 MHz, CDCl3) δ ppm 1.93-2.45 (6H, m), 3.47 (3H, s), 3.70 (1H, m), 7.00 (1H, s), 7.47 (1H, d), 8.58 (1H, dd), 9.08 (1H, d),

MS(FAB)m/z 433 (M+ +1).

Elemental analysis value of C19H15N6OS;

Theoretical value (%) C, 52.77, H, 3.50, N, 19.44.

Measured values (%) C, 53.10, H, 3.83, N, 19.61.

(0264)

Example 63

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methylamino phenyl)-1H-tetrazole

0.5N sodium carbonate aqueous solution 3 ml and methanol 3 ml were added to 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-(N-methyl-N-trifluoroacetyl) aminophenyl)-1H-tetrazole 160

mg, and the mixture was stirred at room temperature for five hours. The reaction liquor was discharged into 0.5N hydrochloric acid 10 ml, and precipitated crystals were recovered by filtration. The crude crystals were recrystallised from chloroform-ethanol, and the title substance was obtained as needle crystals.
mp. 157-161°C.
IR v max cm-1 2216. NMR (400 MHz, CDCl3) δ ppm 1.92-2.45 (6H, m), 2.99 (3H, s), 3.70 (1H, m), 4.84 (1H, br), 6.72 (1H, d), 6.94 (1H, s), 8.16 (1H, br d), 8.62 (1H, br s),
MS(FAB)m/z 337 (M+ +1).

(0265)

Example 64

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-trifluoro aceto aminophenyl)-1H-tetrazole

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-trifluoro aceto amino) benzonitrile was treated in the same way as in Step 2 of Example 62, and the title substance was obtained.
mp. 210-212°C (recrystallization solvent : chloroform-ethanol).
NMR (400 MHz, DMSO-d6) δ ppm 1.85-2.40 (6H, m), 3.70 (1H, m), 7.14 (1H, s), 7.76 (1H, s), 7.78 (1H, dd), 8.47 (1H, d), 8.70 (1H, d), 12.59 (1H, s),
MS(FAB)m/z 418 (M+ +1).
Elemental analysis value of C18H13F3 N6 OS;
Theoretical value (%) C, 51.67, H, 3.13, N, 20.09
Measured values (%) C, 51.51, H, 3.33, N, 19.97.

(0266)

Example 65

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-aminophenyl)-1H-tetrazole

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-trifluoro aceto aminophenyl)-1H-tetrazole was treated in the same way as in Example 63, and the title substance was obtained.
mp. 128-136°C (recrystallization solvent : chloroform-ethanol-n-hexane).
IR v max cm-1 2196. NMR (400 MHz, CDCl3) δ ppm 1.83-2.45 (6H, m), 3.83 (1H, m), 6.72 (1H, d), 7.04 (1H, s), 7.27 (1H, m), 8.03 (1H, d),
MS(FAB)m/z 323 (M+ +1).
Elemental analysis value of C16H14N6S;
Theoretical value (%) C, 59.61, H, 4.38, N, 26.07
Measured values (%) C, 59.78, H, 4.79,N, 25.24.

(0267)

Example 66

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-acetoxymethyl phenyl)-1H-tetrazole

Step 1

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-acetoxymethyl benzonitrile.

5-(3-iodo-2-acetoxymethyl) benzonitrile and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-acetoxymethyl benzonitrile was obtained.

mp. 84-87°C (recrystallization solvent : chloroform-n-hexane).

NMR (400 MHz, CDCl3) δ ppm 1.87-2.45 (6H, m), 3.71 (1H, m), 5.49 (2H, s), 7.03 (1H, s), 7.49 (1H, t), 7.72 (1H, d), 7.85 (1H, d),

MS(FAB)m/z 337 (M+ +1).

Elemental analysis value of C19H16N2O2S•1/4H2O;

Theoretical value (%) C, 66.94, H, 4.88, N, 8.22

Measured values (%) C, 66.80, H, 4.83, N, 7.78.

(0268)

Step 2

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-acetoxymethyl benzonitrile was treated in the same way as in Step 2 of Example 62, and the title substance was obtained.

mp. 128-136°C (recrystallization solvent : chloroform-ethanol-n-hexane).

IR v max cm-1 2232, 1716. NMR (400 MHz, CDCl3) δ ppm 1.76-2.32 (6H, m), 1.95 (3H, s), 3.55 (1H, m), 5.25 (1H, d), 6.88 (1H, s), 7.55 (1H, t), 7.81 (1H, m), 7.85 (1H, m),

MS(FAB)m/z 380 (M+ +1).

Elemental analysis value of C19H17N5O2S;

Theoretical value (%) C, 60.19, H, 4.52,N, 18.46

Measured values (%) C, 60.61, H, 4.81, N, 18.48.

(0269)

Example 67

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-hydroxymethyl phenyl)-1H-tetrazole

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-acetoxymethyl phenyl)-1H-tetrazole was treated in the same way as in Example 63, and the title substance was obtained.

mp. 255-259°C (recrystallization solvent : chloroform-ethanol).

NMR (400 MHz, DMSO-d6) δ ppm 1.95-2.48 (6H, m), 3.50 (1H, m), 5.83 (2H, s), 7.53 (1H, br s), 7.67 (1H, t), 8.04 (1H, t), 8.17 (1H, br s), 8.72 (1H, d),

MS(FAB)m/z 338 (M+ +1).

Elemental analysis value of C17H15N5OS•1/2H2O;

Theoretical value (%) C, 58.94, H, 4.66, N, 20.21,
Measured values (%) C, 58.72, H, 4.46, N, 20.24.

(0270)

Example 68

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-acetyl-2H-tetrazole

Acetic anhydride.5 ml and pyridine 1 ml were added to 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole 615 mg, and the mixture was stirred at room temperature for 15 hours. The reaction liquor was discharged into 1N hydrochloric acid 100 ml, and precipitated crystals were recovered by filtration and, after washing with water, it was dried. The crude crystals were recrystallised from ether-n-hexane, and 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-acetyl-2H-tetrazole was obtained.
mp. 110-112°C.
IR v max cm-1 2216, 1778. NMR (400 MHz, DMSO-d6) δ ppm 1.90-2.42 (6H, m), 3.03 (3H, s), 3.69-3.76 (1H, m), 6.99 (1H, s), 7.56 (1H, t), 7.67 (1H, dt), 8.30 (1H, dt), 8.52 (1H, t),
MS(EI)m/z 349(M+).
Elemental analysis value of C18H15N5OS;
Theoretical value (%) C, 61.87, H, 4.33, N, 20.04,
Measured values (%) C, 61.87, H, 4.49, N, 20.06..

(0271)

Example 69

3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4H-(1,2,4) oxadiazole-5-one

Step 1

Synthesis of 3-(3-iodo phenyl)-4-(4-methoxybenzyl)-(1,2,4) oxadiazole-5-one

3-(3-iodo phenyl)-4H-(1,2,4) oxadiazole-5-one was processed in the same way as in Step 3 of Example 1, and 3-(3-iodo phenyl)-4-(4-methoxybenzyl)-(1,2,4) oxadiazole-5-one was obtained as a straw-coloured oily substance.
NMR (400 MHz, CDCl3) δ ppm 3.80 (3H, s), 4.74 (2H, s), 6.84-6.86 (2H, m), 7.03-7.05 (2H, m), 7.23 (1H, t), 7.41 (1H, d), 7.73 (1H, s), 7.91 (1H, d).

(0272)

Step 2

Synthesis of 3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(4-methoxybenzyl)-(1,2,4) oxadiazole-5-one.

3-(3-iodo phenyl)-4-(4-methoxybenzyl)-(1,2,4) oxadiazole-5-one and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 3-(3-[2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(4-methoxybenzyl)-(1,2,4) oxadiazole-5-one was obtained as a straw-coloured oily substance.
NMR (400 MHz, CDCl3) δ ppm 1.90-2.40 (6H, m), 3.68-3.79 (1H, m), 3.76 (3H, s), 4.77 (2H, s), 6.81-6.83 (2H, m), 7.01 (1H, s), 7.01-7.03 (2H, m), 7.45 (1H, d), 7.50 (1H, t), 7.65 (1H, s), 7.77 (1H, d).

(0273)

Step 3

Synthesis of 3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4H-(1,2,4) oxadiazole-5-one.
3-(3-[2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(4-methoxybenzyl)-(1,2,4) oxadiazole-5-one was processed in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 246-249°C (recrystallization solvent : chloroform-n-hexane).
IR v max cm-1 2224, 1782. NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.34 (6H, m), 3.64-3.72 (1H, m), 7.57 (1H, s), 7.69 (1H, t), 7.91 (1H, d), 7.92 (1H, d), 8.07 (1H, s), 13.01 (1H, s).
MS(EI)m/z 323(M+).
Elemental analysis value of C17H13N3 O2 S;
Theoretical value (%) C, 63.14, H, 4.05, N, 12.99,
Measured values (%) C, 62.74, H, 4.07, N, 12.61..

(0274)

Example 70

(Z)-5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzylidene)-2-thioxo thiazolidin-4-on

Step 1

Synthesis of 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzaldehyde.
3-iodo benzaldehyde and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzaldehyde was obtained.
mp. 77-79°C. NMR (400 MHz, CDCl3) δ ppm 1.89-2.43 (6H, m), 3.67-3.75 (1H, m), 6.99 (1H, s), 7.56 (1H, t), 7.83 (1H, dt), 7.91 (1H, dt), 8.09 (1H, t), 10.02 (1H, s).

(0275)

Step 2

Synthesis of (Z)-5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzylidene)-2-thioxo thiazolidin-4-one.

Acetic acid 20 ml was added to 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzaldehyde 535 mg, rhodanine 266 mg and sodium acetate 656 mg, and the mixture was heated under reflux for four hours. After cooling, the reaction liquor was discharged into water 200 ml, and the precipitated crystals were recovered. It was refined by silica gel column chromatography (eluate = chloroform : ethyl acetate = 20 : 1), and this was recrystallised from chloroform-n-hexane, and the title substance was obtained as straw-coloured crystalline powder.
mp. 198-201°C.
IR v max cm-1 2208, 1732. NMR (400 MHz, CDCl3) δ ppm 1.91-2.41 (6H, m), 3.69-3.77 (1H, m), 7.00 (1H, s), 7.49-7.51 (2H, m), 7.63 (1H, s), 7.64-7.67 (1H, m), 7.69 (1H, s), 9.77 (1H, s).
MS(EI)m/z 382(M+).
Elemental analysis value of C19H14N2OS3;
Theoretical value (%) C, 59.66, H, 3.69, N, 7.32,
Measured values (%) C, 59.52, H, 3.66, N, 7.22.

(0276)

Example 71

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-(1,2,4) oxadiazolin-3-one

Step 1

Synthesis of 5-(3-iodo phenyl)-2-(4-methoxybenzyl)-(1,2,4) oxadiazolin-3-one.
5-(3-iodo phenyl)-(1,2,4) oxadiazolin-3-one was processed in the same way as in Step 3 of Example 1, and 5-(3-iodo phenyl)-2-(4-methoxybenzyl)-(1,2,4) oxadiazolin-3-one was obtained as reddish brown oily substance.
NMR (400 MHz, CDCl3) δ ppm 3.80 (3H, s), 5.32 (2H, s), 6.92 (2H, d), 7.42 (1H, d), 7.85 (1H, d), 7.94 (1H, t), 8.06 (1H, d), 8.43 (1H, s).

(0277)

Step 2

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-(1,2,4) oxadiazolin-3-one.
5-(3-iodo phenyl)-2-(4-methoxybenzyl)-(1,2,4) oxadiazolin-3-one and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(3-[2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-(1,2,4) oxadiazolin-3-one was obtained as reddish brown oily substance.
NMR (400 MHz, CDCl3) δ ppm 1.90-2.00 (1H, m), 2.00-2.10 (1H, m), 2.20-2.40 (4H, m), 3.60-3.80 (1H, m), 3.82 (3H, s), 5.34 (2H, s), 6.92 (2H, d), 6.99 (1H, s), 7.44 (2H, d), 7.53 (1H, t), 7.78 (1H, d), 8.09 (1H, d), 8.30 (1H, s).

(0278)

Step 3

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-(1,2,4) oxadiazolin-3-one.

5-(3-[2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-(1,2,4) oxadiazolin-3-one was processed in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 208-212°C (recrystallization solvent : chloroform-methanol-n-hexane).

IR v max cm-1 1600, 1470, 1380, 1248, 1136. NMR (400 MHz, DMSO-d6) δ ppm 1.80-1.90 (1H, m), 1.90-2.10 (1H, m), 2.20-2.40 (4H, m), 3.60-3.80 (1H, m), 7.55 (1H, s), 7.61 (1H, t), 7.88 (1H, d), 8.03 (1H, d), 8.25 (1H, s), 10.66 (1H, br s).

MS(FAB)m/z 324 (M+ +1).

Elemental analysis value of C17H13N3O2S•0.475H2O;

Theoretical value (%) C, 61.51, H, 4.24,N, 12.66,

Measured values (%) C, 61.92, H, 4.64, N, 12.50.

(0279)

Example 72

3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-5-hydroxyisoxazole

3-(3-iodo phenyl)-5-hydroxyisoxazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and the title substance was obtained.

mp. 143-148°C (recrystallization solvent : chloroform-n-hexane). NMR (400 MHz, CDCl3) δ ppm 1.90-2.00 (1H, m), 2.00-2.10 (1H, m), 2.20-2.40 (4H, m), 3.60-3.80 (1H, m), 4.20 (2H, ds), 6.99 (1H, s), 7.54 (1H, t), 7.56 (1H, d), 7.63 (1H, s), 7.66 (1H, d).

MS(FAB)m/z 323 (M+ +1).

(0280)

Example 73

2-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-(1, 3,4) oxadiazolin-5-one

2-(3-iodo phenyl)-(1,3,4) oxadiazolin-5-one and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and the title substance was obtained.

mp. 186-190°C. NMR (400 MHz, DMSO-d6) δ ppm 1.90-2.00 (1H, m), 2.00-2.10 (1H, m), 2.20-2.50 (4H, m), 3.60-3.80 (1H, m), 7.00 (1H, s), 7.50 (1H, t), 7.71 (1H, d), 7.85 (1H, d), 8.08 (1H, s),

MS(FAB)m/z 324 (M+ +1).

Elemental analysis value of C17H13N3O2S•0.3H2O;

Theoretical value (%) C, 63.44, H, 4.02, N, 12.33,

Measured values (%) C, 63.15, H, 4.24, N, 12.34.

(0281)

Example 74

2-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-(1,2,4) oxadiazolidine-3,5-dione

2-(3-iodo phenyl)-(1,2,4) oxadiazolidine-3,5-dione and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and the title substance was obtained.

mp. 141-145°C (decomp).

IR v max cm-1 1738, 1574, 1358, 1182. NMR (400 MHz, DMSO-d6) δ ppm 1.90-2.00 (1H, m), 2.00-2.10 (1H, m) .2.20-2.40 (4H, m), 3.60-3.80 (1H, m), 6.96 (1H, s), 7.48 (1H, t), 7.61 (1H, d), 8.14 (1H, d), 8.47 (1H, s).

MS(FAB)m/z 340 (M+ +1).

(0282)

Example 75

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzylidene) thiazolidine-2,4-dione

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzaldehyde and 2,4-thiazolin dione were treated in the same way as in Example 70, and the title substance was obtained.

mp. 198-201°C (recrystallization solvent : chloroform-n-hexane).

IR v max cm-1 2212, 1748. NMR (400 MHz, CDCl3) δ ppm 1.89-2.44 (6H, m), 3.69-3.77 (1H, m), 7.00 (1H, s), 7.47-7.53 (2H, m), 7.63-7.65 (1H, m), 7.73 (1H, s), 7.83 (1H, s), 9.09 (1H, s),

MS(EI)m/z 366(M+).

Elemental analysis value of $C19H19N2O2S_2 \cdot 1/4H2O$;

Theoretical value (%) C, 61.52, H, 3.94, N, 7.55,

Measured values (%) C, 61.51,H, 3.89, N, 7.31.

(0283)

Example 76

1-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4H-tetrazolin-5-one

Step 1

Synthesis of 1-(3-iodo phenyl)-4-(2-(trimethylsilyl) ethoxy) methyl-4H-tetrazolin-5-one.

DMF 5 ml was added to 1-(3-iodo phenyl)-4H-tetrazolin-5-one 202 mg and potassium carbonate 152 mg, and with stirring at 0°C, (2-chloromethoxy ethyl) trimethylsilane 133 mg was added. It was stirred at the same temperature for 30 minutes and at room temperature for two hours. The reaction liquor was discharged into water 100 ml, and extraction was carried out with ethyl acetate. The liquid extract was washed with saturated aqueous sodium chloride solution and

thereafter, was dried with sodium sulfate. The solvent was eliminated by distillation, and the obtained residue was refined by column chromatography using silica gel (eluate = chloroform : n-hexane =1:1), and 1-(3-iodo phenyl)-4-(2-(trimethylsilyl) ethoxy) methyl-4H-tetrazolin-5-one was obtained as an oily substance.

NMR (400 MHz, CDCl3) δ ppm 0.03 (9H, s), 0.99 (2H, t), 3.75 (2H, t), 5.39 (2H, s), 7.24 (1H, t), 7.70-7.73 (1H, m), 7.97-7.99 (1H, m), 8.35 (1H, s).

(0284)

Step 2

Synthesis of 1-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4H-tetrazolin-5-one.

1-(3-iodo phenyl)-4-(2-(trimethylsilyl) ethoxy) methyl-4H-tetrazolin-5-one and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and continuing, DMF 3 ml, tetrabutyl ammonium fluoride (THF solution of 1.0M) 1 ml were added to this, and the mixture was stirred at 60°C for two hours. The reaction liquor was discharged into 1N hydrochloric acid 100 ml, and precipitated crystals were recovered by filtration. The crude crystals were recrystallised from chloroform-n-hexane, and the title substance was obtained as a pale-brown crystalline powder.

mp. 196-199°C.

IR v max cm-1 2212, 1742. NMR (400 MHz, DMSO-d6) δ ppm 1.91-2.46 (6H, m), 3.71-3.80 (1H, m), 7.01 (1H, s), 7.52 (1H, t), 7.59 (1H, d), 7.99 (1H, d), 8.33 (1H, s),

MS(FAB)m/z 323 (M+ +1).

Elemental analysis value of C16H13N5OS;

Theoretical value (%) C, 59.43, H, 4.05, N, 21.66,

Measured values (%) C, 59.06, H, 4.09, N, 21.33..

(0285)

Example 77

4-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1 or 2 or 3H-(1,2,3)-triazole:

Step 1

Synthesis of ethyl 4-(3-bromo phenyl)-1H-(1,2,3)-triazole-5-carboxylate.

Sodium azide 1.11 g was suspended in DMF 10 ml, and aluminum chloride 1.45 was gradually added while stirring under ice-cooling. The reaction liquor was stirred at room temperature for one hour, and thereafter, DMF 5 ml solution of ethyl propiolate ester1.3 g was added dropwise over a period of five minutes. The reaction liquor was stirred at room temperature for one hour and thereafter, further stirred at 60°C for 30 minutes. After cooling, the reaction liquor was discharged in ice 100 ml and 2M hydrochloric acid 50 ml. The precipitated crystals were

recovered by filtration, and it was air-dried. The crude crystals were dissolved in chloroform and refined by column chromatography using silica gel (eluate = chloroform : ethanol = 8 : 2), and 4-(3-bromo phenyl)-1H-(1,2,3)-triazole 1.52 g was obtained.
NMR (400 MHz, CDCl3) δ ppm 1.39 (3H, t), 4.44 (2H, q), 7.34 (1H, t), 7.58 (1H, m), 7.84 (1H, d), 8.05 (1H, br s).

(0286)

Step 2

Synthesis of ethyl 4-(3-bromo phenyl)-1-(4-methoxybenzyl)-1H-(1,2,3)-triazole-5-carboxylate, ethyl 4-(3-bromo phenyl)-2-(4-methoxybenzyl)-2H-(1,2,3)-triazole-5-carboxylate and ethyl 4-(3-bromo phenyl)-3-(4-methoxybenzyl)-3H-(1,2,3)-triazole-5-carboxylate.

Ethyl 4-(3-bromo phenyl)-1H-(1,2,3)-triazole-5-carboxylate is processed in the same way as in Step 3 of Example 1, and ethyl 4-(3-bromo phenyl)-1-(4-methoxybenzyl)-1H-(1,2,3)-triazole-5-carboxylate, ethyl 4-(3-bromo phenyl)-2-(4-methoxybenzyl)-2H-(1,2,3)-triazole-5-carboxylate and ethyl 4-(3-bromo phenyl)-3-(4-methoxybenzyl)-3H-(1,2,3)-triazole-5-carboxylate were obtained as mixture of 1 position, 2 position and 3 position.
NMR (400 MHz, CDCl3) δ ppm 1.24-1.34 (3H, m), 3.78 (3H, s), 4.25-4.45 (2H, m), 5.59-5.87 (2H, series of s), 6.83-7.97 (8H, m).

(0287)

Step 3

Synthesis of 4-(3-iodo phenyl)-1H-(4-methoxybenzyl)-1H-(1,2,3)-triazole or 4-(3-iodo phenyl)-2-(4-methoxybenzyl)-2H-(1,2,3)-triazole or 4-(3-iodo phenyl)-3-(4-methoxybenzyl)-3H-(1,2,3)-triazole.

Bromide of Step 3 was treated same as in Step 2 of Example 19, and it was purified by column chromatography using silica gel (eluate = n-hexane : ethyl acetate = 5 : 1), and 4-(3-iodo phenyl)-2-(4-methoxybenzyl)-2H-(1,2,3)-triazole or 4-(3-iodo phenyl)-3-(4-methoxybenzyl)-3H-(1,2,3)-triazole or 4-(3-iodo phenyl)-1H-(4-methoxybenzyl)-1H-(1,2,3)-triazole deesterified at the same time as halogen exchange with single isomer of 1 position, 2 position or 3 position was obtained as an oily substance.
NMR (400 MHz, CDCl3) δ ppm 3.82 (3H, s), 5.51 (2H, s), 6.93 (2H, d), 7.13 (1H, t), 7.27 (2H, d), 7.60 (1H, m), 7.70 (1H, d), 8.12 (1H, m).

(0288)

Step 4

Synthesis of 4-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1 or 2 or 3-(4-methoxybenzyl)-1H-(1,2,3)-triazole.

4-cyclobutyl-2-ethinyl thiazole and iodo body obtained in Step 3 were treated in the same way as in Step 4 of Example 1, and 4-(3-[2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1-(4-methoxybenzyl)-1H-(1,2,3)-triazole, 4-(3-[2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-(1,2,3)-triazole or 4-(3-[2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(4-methoxybenzyl)-3H-(1,2,3)-triazole was obtained as an oily substance.
NMR (400 MHz, CDCl3) δ ppm 1.85-2.43 (6H, m), 3.69 (1H, m), 3.83 (3H, s), 5.52 (2H, s), 6.94 (2H, d), 6.96 (1H, s), 7.28 (2H, d), 7.42 (1H, t), 7.53 (1H, m), 7.63 (1H, s), 7.88 (1H, m), 7.95 (1H, t).

(0289)

Step 5

Synthesis of 4-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1H-(1,2,3)-triazole.

Compound obtained in the aforesaid Step 3 was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 146-150°C (recrystallization solvent : chloroform-n-hexane).
IR v max cm-1 2216. NMR (400 MHz, CDCl3) δ ppm 1.85-2.45 (6H, m), 3.71 (1H, m), 6.97 (1H, s), 7.47 (1H, t), 7.59 (1H, d), 7.87 (1H, d), 7.79 (1H, s), 8.05 (1H, br),
MS(EI)m/z 306(M+).
Elemental analysis value of C17H14N4S•1/5H2O;
Theoretical value (%) C, 65.68, H, 4.70, N, 18.02,
Measured values (%) C, 65.83, H, 4.67, N, 17.55..

(0290)

Example 78

Ethyl 4-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1H-(1,2,3)-triazole-5-carboxylate

Step 1

Synthesis of ethyl 3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl propiolic acid.

Ethyl 3-iodo phenyl propiolic acid and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and ethyl 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl propiolic acid was obtained as reddish brown oily substance.
NMR (400 MHz, CDCl3) δ ppm 1.37 (3H, t), 1.85-2.45 (6H, m), 3.70 (1H, m), 4.31 (2H, q), 6.98 (1H, s), 7.38 (1H, t), 7.59 (1H, d), 7.65 (1H, d), 7.79 (1H, s).

(0291)

Step 2

Synthesis of ethyl 4-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1H-(1,2,3)-triazole-5-carboxylate.

Ethyl 3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl propiolic acid was processed in the same way as in Step 1 of Example 77, and the title substance was obtained.

mp. 142-145°C (recrystallization solvent : chloroform-n-hexane).

IR v max cm-1 2216, 1712. NMR (400 MHz, CDCl3) δ ppm 1.37 (3H, t), 1.85-2.45 (6H, m), 3.73 (1H, m), 4.42 (2H, q), 6.99 (1H, s), 7.45 (1H, t), 7.62 (1H, d), 7.89 (1H, d), 7.99 (1H, s), MS(EI)m/z 378(M+).

Elemental analysis value of C20H18N4O2S;

Theoretical value (%) C, 63.47, H, 4.79, N, 14.81,

Measured values (%) C, 63.37, H, 4.90,N, 14.55..

(0292)

Example 79

4-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1H-(1,2,3)-triazole-5-carboxylic acid

Ethyl 4-(3-[2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1H-(1,2,3)-triazole-5-carboxylate was processed in the same way as in Example 56, and the title substance was obtained.

mp. 142-145°C (recrystallization solvent : chloroform-ethanol).

IR v max cm-1 2216, 1740. NMR (400 MHz, DMSO-d6) δ ppm 1.85-2.40 (6H, m), 3.68 (1H, m), 7.32 (1H, s), 7.54 (1H, t), 7.65 (1H, m), 7.95 (1H, br), 8.09 (1H, br),

MS(EI)m/z 350(M+).

Elemental analysis value of C18H14N4O2S;

Theoretical value (%) C, 61.70, H, 4.03, N, 15.99,

Measured values (%) C, 61.84, H, 4.27, N, 15.71..

(0293)

Example 80

4-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1-methyl-1H-(1,2,3)-triazole-5-carboxylic acid

Step 1

Synthesis of ethyl 4-(3-[2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1-methyl-1H-(1,2,3)-triazole-5-carboxylate and ethyl 4-(3-[2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-methyl-2H-(1,2,3)-triazole-5-carboxylate.

Using methyl iodide instead of 4-methoxybenzyl chloride in Step 3 of Example 1, ethyl 4-(3-[2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1H-(1,2,3)-triazole-5-carboxylate was treated in the same way, and as mixture of 1-position : 2-position is approx 1 : 1, ethyl 4-(3-[2-(4-cyclobutyl-2-

thiazolyl) ethinyl) phenyl)-1-methyl-1H-(1,2,3)-triazole-5-carboxylate and ethyl 4-(3-[2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-methyl-2H-(1,2,3)-triazole-5-carboxylate were obtained as an oily substance.
NMR (400 MHz, CDCl3) δ ppm 1.32 and 1.39 (3H, each t), 1.85-2.45 (6H, m), 3.70 (1H, m), 4.31 and 4.36 (3H, each s), 4.37 ans4.43 (2H, each q), 6.96 (1H, s), 7.46 (1H, t), 7.64 (1H, br d), 7.78 and 7.88 (1H, each br d), 7.97 and 8.07 (1H, each br s).

(0294)

Step 2

Synthesis of 4-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1-methyl-1H-(1,2,3)-triazole-5-carboxylic acid.

Mixture of the aforesaid 1-methyl body and 2-methyl body was treated in the same way as in Example 56, and it was recrystallised from chloroform-n-hexane, and the title substance was obtained.
mp. 142-145°C,
IR v max cm-1 2216,
NMR (400 MHz, DMSO-d6) δ ppm 1.82-2.35 (6H, m), 3.68 (1H, m), 4.18 (3H, s), 7.49 (1H, t), 7.53 (1H, s), 7.62 (1H, d), 8.13 (1H, d), 8.44 (1H, s),
MS(EI)m/z 364(M+).

(0295)

Example 81

4-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-methyl-2H-(1,2,3)-triazole-5-carboxylic acid

4-(3-[2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-methyl-2H-(1,2,3)-triazole-5-carboxylate was processed in the same way as in Example 56, and the title substance was obtained.
mp. 142-145°C,
IR v max cm-1 2216,
NMR (400 MHz, DMSO-d6) δ ppm 1.82-2.35 (6H, m), 3.67 (1H, m), 4.10 (3H, s), 7.48 (1H, t), 7.53 (1H, s), 7.57 (1H, d), 8.17 (1H, d), 8.37 (1H, s),
MS(EI)m/z 364(M+).

(0296)

Example 82

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1-(2-methoxyethoxy) methyl-1H-(1,2,3)-triazole-4-carboxylic acid:

Step 1

Synthesis of ethyl 5-(3-iodo phenyl)-1-(2-methoxyethoxy) methyl-1H-(1,2,3)-triazole-4-carboxylate, ethyl 5-(3-iodo phenyl)-2-(2-methoxyethoxy) methyl-2H-(1,2,3)-triazole-4-carboxylate and ethyl 5-(3-iodo phenyl)-3-(2-methoxyethoxy) methyl-3H-(1,2,3)-triazole-4-carboxylate.

Using 2-(2-methoxyethoxy) methyl chloride instead of 4-methoxybenzyl chloride of Step 3 in Example 1, and ethyl 5-(3-iodo phenyl)-1H-(1,2,3)-triazole-4-carboxylate was treated in the same way, and mixture of 1, 2 and 3 position, ethyl 5-(3-iodo phenyl)-1-(2-methoxyethoxy) methyl-1H-(1,2,3)-triazole-4-carboxylate, ethyl 5-(3-iodo phenyl)-2-(2-methoxyethoxy) methyl-2H-(1,2,3)-triazole-4-carboxylate and ethyl 5-(3-iodo phenyl)-3-(2-methoxyethoxy) methyl-3H-(1,2,3)-triazole-4-carboxylate were obtained as an oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.25-1.42 (3H, m), 3.25-3.40 (3H, series of s), 3.36 (1H, s), 3.54 (2H, m), 3.49-3.85 (4H, m), 4.30-4.48 (2H, m), 5.80-6.12 (3H, series of s), 7.15-8.23 (4H, m).

(0297)

Step 2

Synthesis of ethyl 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1-(2-methoxyethoxy) methyl-1H-(1,2,3)-triazole-4-carboxylate.

4-cyclobutyl-2-ethinyl thiazole and iodo body obtained in the aforesaid Step 1 were treated in the same way as in Step 4 of Example 1, and product was separated by column chromatography using silica gel (eluate = n-hexane-ethyl acetate = 4 : 1), and ethyl 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1-(2-methoxyethoxy) methyl-1H-(1,2,3)-triazole-4-carboxylate was obtained as an oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.31 (3H, t), 1.88-2.43 (6H, m), 3.36 (3H, s), 3.54 (2H, m), 3.68 (1H, m), 3.82 (2H, m), 4.35 (2H, q), 5.70 (2H, s), 6.97 (1H, s), 7.52 (1H, t), 7.57 (1H, m), 7.74 (1H, m), 7.76 (1H, m).

(0298)

Step 3

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1-(2-methoxyethoxy) methyl-1H-(1,2,3)-triazole-4-carboxylic acid.

Ethyl 5-(3-[2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1-(2-methoxyethoxy) methyl-1H-(1,2,3)-triazole-4-carboxylate was processed in the same way as in Example 56, and the title substance was obtained.

mp. 143-146°C (recrystallization solvent : chloroform-n-hexane),

NMR (400 MHz, DMSO-d6) δ ppm 1.82-2.38 (6H, m), 3.23 (3H, s), 3.43 (2H, m), 3.64 (3H, m), 5.61 (2H, s), 7.41 (1H, s), 7.59 (1H, t), 7.67 (1H, br d), 7.75 (1H, br d), 7.84 (1H, br s),

MS(EI)m/z 439 (M+ +1).

(0299)

Example 83

5-(2-(3-(2-[4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-thiazolyl)-1H-tetrazole

Step 1

Synthesis of 5-(2-(3-iodo phenyl)-4-thiazolyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(2-(3-iodo phenyl)-4-thiazolyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(2-(3-iodo phenyl)-4-thiazolyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 173-176°C (recrystallization solvent : chloroform-n-hexane),

NMR (400 MHz, CDCl3) δ ppm 3.76 (3H, s), 6.13 (2H, s), 6.84-6.87 (2H, m), 7, 25 (1H, t), 7.31-7.34 (2H, m), 7.84 (1H, d), 7.93 (1H, d), 8.32 (1H, s), 8.35 (1H, s),

MS(EI)m/z 475 (M+ +1),

Elemental analysis values as C18H14IN4OS

Theoretical values (%) C, 45.49, H, 2.97, N, 14.73,

Measured values (%) C, 45.46, H, 3.06, N, 14.74.

(0300)

Step 2

Synthesis of 5-(2-(3-(2-[4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-thiazolyl)-1H-tetrazole.

5-(2-(3-(2-[4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-thiazolyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and continuing, it was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 156-159°C (decomp) (recrystallization solvent : chloroform)

IR v·max cm-1 2216,

NMR (400 MHz, DMSO-d6) δ ppm 1.88-2.33 (6H, m), 3.65-3.73 (1H, m), 7.57 (1H, s), 7, 69 (1H, t), 7.84 (1H, d), 8.17 (1H, d), 8.39 (1H, s), 8.66 (1H, s),

MS(FAB)m/z 391 (M+ +1),

Elemental analysis values as C19H14N6S2

Theoretical values (%) C, 58.44, H, 3.61, N, 21.52,

Measured values (%) C, 58.60, H, 3.34, N, 21.55.

(0301)

Example 84

3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) benzoic acid:

Step 1

Synthesis of 3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-1-bromobenzene.

4-cyclobutyl-2-ethinyl thiazole and 1-bromo-3-iodobenzene were treated in the same way as in Step 4 of Example 1, and 3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-1-bromobenzene was obtained as an oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.85-2.45 (6H, m), 3.70 (1H, m), 6.97 (1H, s), 7.24 (1H, t), 7.52 (1H, m), 7.74 (1H, s).

(0302)

Step 2

Synthesis of 3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) benzaldehyde.

2Mcm-1 sodium carbonate aqueous solution 3.5 ml and 1,2-dimethoxyethane 25 ml were added to 3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-1-bromobenzene 600 mg, 3-formylphenyl boronic acid 232 mg and tetrakis (triphenyl phosphine) (0) palladium 109 mg, and the mixture was heated under reflux for two hours. After cooling, water 100 m was added. It was extracted with methylene chloride. The extract layer was washed with saturated aqueous sodium chloride solution and thereafter, was dried with sodium sulfate. The residue obtained by elimination by distillation of the solvent was separated by column chromatography using silica gel (eluate = n-hexane-ethyl acetate = 3 : 1), and 3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) benzaldehyde 325 mg was obtained as an oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.85-2.45 (6H, m), 3.71 (1H, m), 6.97 (1H, s), 7.49 (1H, t), 7.58-7.67 (3H, m), 7.84-7.92 (3H, m), 8.12 (1H, t), 10.11 (1H, s).

(0303)

Step 3

Synthesis of 3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) benzonitrile.

5 ml of formic acid was added to 3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) benzaldehyde 300 mg, hydroxylamine hydrochloride 65 mg and sodium formate 119 mg, and the mixture was heated under reflux for two hours. After cooling, water 50 ml was added to the reaction liquor and extraction was carried out with methylene chloride. The extract layer was washed with saturated aqueous sodium chloride solution and thereafter, was dried with sodium sulfate. The residue obtained by elimination by distillation of the solvent was separated by column chromatography using silica gel (eluate = n-hexane-ethyl acetate = 9 : 1), and 3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) benzonitrile 280 mg was obtained as an oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.87-2.45 (6H, m), 3.71 (1H, m), 6.98 (1H, s), 7.48 (1H, t), 7.54-7.94 (7H, m).

(0304)

Step 4

Synthesis of 3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) benzoic acid.

4N sodium hydroxide aqueous solution 5 ml and ethanol 10 ml were added to 3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) benzonitrile 250 mg, and the mixture was heated under reflux for five hours. After cooling, the reaction liquor was discharged into 1N hydrochloric acid 50 ml, and the precipitated crystals were recovered by filtration and, after washing with water, it was dried. The crude crystals were recrystallised from chloroform-ethanol, and the title substance was obtained as minute prism crystals.

mp. 119-120°C,

IR v max cm-1 2216, 1694,

NMR (400 MHz, CDCl3) δ ppm 1.85-2.45 (6H, m), 3.71 (1H, m), 6.97 (1H, s), 7.45-8.14 (7H, m), 8.35 (1H, br s),

MS(EI)m/z 359(M+),

Elemental analysis values as C22H17N2S

Theoretical values (%) C, 73.51,H, 4.77, N, 3.90,

Measured values (%) C, 73.80, H, 5.00, N, 3.52.

(0305)

Example 85

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-ethyl isoxazole-4-carboxylic acid:

Step 1

Synthesis of 5-(3-iodo phenyl)-3-ethyl isoxazole-4-carboxylate.

To ethyl 3-iodo propiolic acid 750 mg, 4-chlorophenyl isocyanic acid 1.19 g, 1-nitropropane 334 mg and triethylamine 0.087 ml was added 30 ml benzene and stirred for two days. The insolubles were separated by filtration, and the filtrate was eliminated by distillation. The residue was separated by column chromatography using silica gel (eluate = n-hexane-ethyl acetate = 10 : 1), and 5-(3-iodo phenyl)-3-ethyl isoxazole-4-carboxylate 856 mg was obtained as a straw-coloured oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.33 (3H, t), 1.34 (3H, t), 2.97 (2H, q), 4.31 (2H, q), 7.22 (1H, m), 7.83 (2H, m), 8.22 (1H, d).

(0306)

Step 2

Synthesis of ethyl 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-ethyl isoxazole-4-carboxylate.

5-(3-iodo phenyl)-3-ethyl isoxazole-4-carboxylate and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and ethyl 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-ethyl isoxazole-4-carboxylate was obtained as an oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.33 (3H, t), 1.36 (3H, t), 1.85-2.45 (6H, m), 2.98 (2H, q), 3.70 (1H, m), 4.33 (2H, q), 6.97 (1H, s), 7.49 (1H, t), 7.72 (1H, d), 7.89 (1H, d), 8.10 (1H, s).

(0307)

Step 3

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-ethyl isoxazole-4-carboxylic acid.

Ethyl 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-ethyl isoxazole-4-carboxylate was processed in the same way as in Example 56, and the title substance was obtained.

mp. 149-150°C (recrystallization solvent : ether),

IR v max cm-1 2224, 1710,

NMR (400 MHz, CDCl3) δ ppm 1.37 (3H, t), 1.85-2.43 (6H, m), 3.01 (2H, q), 3.71 (1H, m), 5.70 (1H, br), 6.98 (1H, s), 7.47 (1H, t), 7.67 (1H, d), 7.92 (1H, d), 8.08 (1H, s),

MS(EI)m/z 378(M+),

Elemental analysis values as C21H18N2O3S•1/2H2O;

Theoretical values (%) C, 65.10, H, 4.94, N, 7.23,

Measured values (%) C, 65.16, H, 4.78, N, 7.08.

(0308)

Example 86

N-(1H-tetrazol-5-yl)-5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-ethyl isoxazole-4-carboxamide

DMF 5 ml was added to 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-ethyl isoxazole-4-carboxylic acid 300 mg, 5-amino-1H-tetrazole 85 mg and 1,1'-carbonyldiimidazole 174 mg, and the mixture was stirred at 80-85°C for five hours. After cooling, the reaction liquor was discharged into water 100 ml, and the precipitated crystals were recovered by filtration. The crude crystals were recrystallised from chloroform-ethanol, and the title substance was obtained.

mp. 265-268°C,

IR v max cm-1 2220, 1682,

NMR (400 MHz, DMSO-d6) δ ppm 1.25 (3H, t), 1.85-2.35 (6H, m), 2.85 (2H, q), 3.67 (1H, m), 7.56 (1H, s), 7.64 (1H, t), 7.86 (2H, d), 8.04 (1H, s), 12.61 (1H, br),

MS(EI)m/z 445(M+),
Elemental analysis values as C22H19N7O2S;
Theoretical values (%) C, 59.31, H, 4.30, N, 22.01,
Measured values (%) C, 59.16, H, 4.30, N, 21.83.

(0309)

Example 87

1-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-methyl-5-(1H-tetrazol-5-yl)-2,4-(1H, 3H)-pyrimidinedione :

1-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-methyl-5-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2,4-(1H, 3H)-pyrimidinedione was processed in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 256-259°C (recrystallization solvent : chloroform-ethanol-n-hexane),
IR v max cm-1 1722, 1658,
NMR (400 MHz, DMSO-d6) δ ppm 1.86-2.02 (2H, m), 2.20-2.31 (4H, m), 3.35 (3H, s), 3.63-3.71 (1H, m), 7.54 (1H, s), 7.62-7.69 (2H, m), 7.77 (1H, d), 7.87 (1H, s), 8.64 (1H, s),
MS(EI)m/z 431(M+),
Elemental analysis values as C21H17N7O2S;
Theoretical values (%) C, 58.45, H, 3.97, N, 22.73,
Measured values (%) C, 58.19, H, 4.03, N, 22.62.

(0310)

Example 88

Ethyl 1-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-5-(1H-tetrazol-5-yl)-2,4-dioxo-3-(1H, 3H)-pyrimidine acate(sic?):

Step 1

Synthesis of ethyl 1-(3-iodo phenyl)-5-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2,4-dioxo-3-(1H,3H)-pyrimidine acate

Ethyl 1-(3-iodo phenyl)-5-(1H-tetrazol-5-yl)-2,4-dioxo-3-(1H, 3H)-pyrimidine acate was processed in the same way as in Step 3 of Example 1, and ethyl 1-(3-iodo phenyl)-5-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2,4-dioxo-3-(1H, 3H)-pyrimidine acate was obtained as amorphous material.
NMR (400 MHz, CDCl3) δ ppm 1.29 (3H, t), 3.78 (3H, s), 4.23 (2H, q), 4.81 (2H, s), 5.75 (2H, s), 6.87-6.89 (2H, m), 7.24 (1H, t), 7.36-7.38 (2H. m), 7.40 (1H, d), 7.77 (1H, s), 7.81 (1H, d), 8.30 (1H, s).

(0311)

Step 2

Synthesis of ethyl 1-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-5-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2,4-dioxo-3-(1H, 3H)-pyrimidine acate

Ethyl 1-(3-iodo phenyl)-5-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2,4-dioxo-3-(1H, 3H)-pyrimidine acate and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and ethyl 1-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-5-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2,4-dioxo-3-(1H, 3H)-pyrimidine acate was obtained as amorphous material.

NMR (400 MHz, CDCl3) δ ppm 1.34 (3H, t), 1.91-2.08 (2H, m), 2.28-2.39 (4H, m), 3.65-3.74 (1H, m), 3.78 (3H, s), 4.30 (2H, q), 4.81 (2H, s), 5.70 (2H, s), 6.86-6.88 (2H, m), 6.99 (1H, s), 7.16-7.18 (2H, m), 7.29 (1H, d), 7.45 (1H, s), 7.49 (1H, t), 7.64-7.67 (1H, m), 7.67 (1H, s).

(0312)

Step 3

Synthesis of ethyl 1-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-5-(1H-tetrazol-5-yl)-2,4-dioxo-3-(1H, 3H)-pyrimidine acate

Ethyl 1-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-5-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2,4-dioxo-3-(1H, 3H)-pyrimidine acate was processed in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 247-249°C (decomp) (recrystallization solvent : chloroform-n-hexane),

IR ν max cm-1 2216, 1752, 1720, 1656, 1602,

NMR (400 MHz, DMSO-d6) δ ppm 1.22 (3H, t), 2.18-2.32 (4H, m), 3.63-3.71 ($ H, m), 4.18 (2H, q), 4.74 (2H, d), 7.55 (1H, s), 7.65 (1H, t), 7.71 (1H, d), 7.79 (1H, d), 7.92 (1H, d), 8.75 (1H, s), MS(EI)m/z 503(M+),

Elemental analysis values as C24H21N7O4S•1/4H2O;

Theoretical values (%) C, 56.74, H, 4.27, N, 19.30,

Measured values (%) C, 56.54, H, 4.28, N, 19.12.

(0313)

Example 89

1-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-methyl-5-(1H-tetrazol-5-yl)-2,4-dioxo-3-(1H, 3H)-pyrimidine acetic acid :

Ethyl 1-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-5-(1H-tetrazol-5-yl)-2,4-dioxo-3-(1H, 3H)-pyrimidine acate was processed in the same way as in Example 56, and the title substance was obtained.

mp. 219-222°C (decomp) (recrystallization solvent : chloroform-ethanol),

IR v max cm-1 2220, 1726, 1666, 1658, 1604,
NMR (400 MHz, DMSO-d6) δ ppm 1.95-2.02 (2H, m), 2.20-2.30 (4H, m), 3.62-3.71 (1H, m), 4.65 (2H, s), 7.54 (1H, s), 7.65 (1H, t), 7.71 (1H, d), 7.79 (1H, d), 7.92 (1H, s), 8.74 (1H, s),
MS(EI)m/z 475(M+),
Elemental analysis values as C22H17N7O4S•3/4H2O;
Theoretical values (%) C, 54.04, H, 3.81, N, 20.05,
Measured values (%) C, 53.91, H, 3.93, N, 19.94.

(0314)

Example 90

1-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(4-methoxybenzyl)-5-(1H-tetrazol-5-yl)-2,4-(1H, 3H)-pyrimidinedione:

Step 1

Synthesis of 1-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(4-methoxybenzyl)-5-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2,4-(1H, 3H)-pyrimidinedione.

1-(3-iodo phenyl)-3-(4-methoxybenzyl)-5-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2,4-(1H, 3H)-pyrimidinedione and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 1-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(4-methoxybenzyl)-5-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2,4-(1H, 3H)-pyrimidinedione was obtained as amorphous material.
NMR (400 MHz, CDCl3) δ ppm 1.91-2.08 (2H, m), 2.28-2.41 (4H, m), 3.65-3.74 (1H, m), 3.77 (3H, s), 3.78 (3H, s), 5.19 (2H, s), 5.76 (2H, s), 6.82-6.88 (4H, m), 6.97 (1H, s), 7.35-7.37 (2H, m), 7.41 (1H, d), 7.50 (1H, t), 7.55-7.57 (2H, m), 7.60 (1H, s), 7.65 (1H, d), 8.26 (1H, s).

(0315)

Step 2

Synthesis of 1-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(4-methoxybenzyl)-5-(1H-tetrazol-5-yl)-2,4-(1H, 3H)-pyrimidinedione.

1-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(4-methoxybenzyl)-5-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2,4-(1H, 3H)-pyrimidinedione was processed in the same way as in Step 5 of Example 1, and the title substance having 4-methoxybenzyl group in 3 position was obtained.
mp. 205-207°C (decomp) (recrystallization solvent : chloroform-n-hexane)
IR v max cm-1 2216, 1718, 1666, 1604,

NMR (400 MHz, DMSO-d6) δ ppm 1.88-2.02 (2H, m), 2.20-2.30 (4H, m), 3.65-3.69 (1H, m), 3.72 (3H, s), 5.08 (2H, s), 6.82-6.91 (2H, m), 7.36-7.38 (2H, m), 7.54 (1H, s), 7.64 (1H, t), 7.71 (1H, d), 7.78 (1H, d), 7.92 (1H, s), 8.67 (1H, s),
MS(EI)m/z 537(M+).

(0316)

Example 91

N-(1H-tetrazol-5-yl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide:

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzoic acid and 5-amino-1H-tetrazole were treated in the same way as in Example 88, and the title substance was obtained.
mp. 244-246°C (decomp) (recrystallization solvent : chloroform-n-hexane),
IR v max cm-1 2220, 1674, 1590,
NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.10 (2H, m), 2.19-2.35 (4H, m), 3.68 (1H, m), 7.56 (1H, s), 7.69 (1H, t), 7.95 (1H, d), 8.17 (1H, d), 8.41 (1H, s), 12.57 (1H, s),
MS(FAB)m/z 351 (M+ +1),
Elemental analysis values as C17H14N6OS;
Theoretical values (%) C, 58.27, H, 4.03, N, 23.98,
Measured values (%) C, 58.10, H, 4.00, N, 23.82.

(0317)

Example 92

N-(1H-tetrazol-5-yl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methoxy benzamide:

Step 1

Synthesis of 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methoxybenzoic acid.
Ethyl 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methoxyphenyl carboxylate obtained in the same way as in Reference Example 18 was processed in the same way as in Reference Example 19, and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methoxybenzoic acid was obtained.
mp. 141-144°C (decomp) (recrystallization solvent : chloroform-n-hexane),
IR v max cm-1 2212, 1700, 1678,
NMR (400 MHz, CDCl3) δ ppm 1.89-2.41 (6H, m), 3.65-3.74 (1H, m), 4.12 (3H, s), 6.96 (1H, s), 7.08 (1H, d), 7.77 (1H, dd), 8.41 (1H, d),
MS(EI)m/z 313(M+),
Elemental analysis values as C17H15N3OS•1/4H2O
Theoretical values (%) C, 64.23, H, 4.91, N, 4.41,
Measured values (%) C, 64.38, H, 4.89,N, 4.16.

(0318)

Step 2

Synthesis of N-(1H-tetrazol-5-yl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methoxy benzamide.

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methoxybenzoic acid and 5-amino-1H-tetrazole were treated in the same way as in Example 88, and the title substance was obtained.

mp. 233-235°C (decomp) (recrystallization solvent : chloroform-n-hexane),

IR v max cm-1 2212, 1680, 1614, 1564, 1528, 1502,

NMR (400 MHz, DMSO-d6) δ ppm 1.88-2.28 (6H, m), 3.63-3.68 (1H, m), 3.94 (3H, s), 7.30 (1H, d), 7.50 (1H, s), 7.84-7.88 (2H, m), 12.01 (1H, s),

MS(EI)m/z 380(M+),

Elemental analysis values as C18H16N6O2S;

Theoretical values (%) C, 56.83, H, 4.24, N, 22.09,

Measured values (%) C, 56.74, H, 4.15, N, 22.35.

(0319)

Example 93

N-(1H-tetrazol-5-yl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-isopropoxy benzamide:

Step 1

Synthesis of 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-isopropoxy benzoic acid.

Isopropyl 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-isopropoxy phenyl carboxylate obtained in the same way as in Reference Example 18 was processed in the same way as in Reference Example 19, and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-isopropoxy benzoic acid was obtained.

mp. 168-170°C (recrystallization solvent : chloroform-n-hexane),

IR v max cm-1 2216, 1738, 1692, 1602, 1500,

NMR (400 MHz, CDCl3) δ ppm 1.52 (6H, d), 1.89-2.41 (6H, m), 3.65-3.72 (1H, m), 4.86-4.96 (1H, m), 6.96 (1H, s), 7.06 (1H, d), 7.74 (1H, dd), 8.43 (1H, d), 10.98 (1H, s),

MS(EI)m/z 341(M+),

Elemental analysis values as C19H19N3OS•1/4H2O;

Theoretical values (%) C, 65.97, H, 5.68,N, 4.05,

Measured values (%) C, 66.09, H, 5.59, N, 3.83.

(0320)

Step 2

Synthesis of N-(1H-tetrazol-5-yl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-isopropoxy benzamide.

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-isopropoxy benzoic acid and 5-amino-1H-tetrazole were treated in the same way as in Example 88, and the title substance was obtained.
mp. 211-214°C (decomp) (recrystallization solvent : chloroform-n-hexane),
IR v max cm-1 2216, 1664, 1592,
NMR (400 MHz, DMSO-d6) δ ppm 1.34 (6H, d), 1.88-2.30 (6H, m), 3.61-3.68 (1H, m), 4.83-4.86 (1H, m), 7.32 (1H, d), 7.50 (1H, s), 7.80 (1H, d), 7.91 (1H, s), 11.88 (1H, br s),
MS(EI)m/z 408(M+),
Elemental analysis values as C20H20N6O2S;
Theoretical values (%) C, 58.81, H, 4.93, N, 20.57,
Measured values (%) C, 58.61, H, 5.05, N, 20.58.

(0321)

Example 94

N-(1H-tetrazol-5-yl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylbenzamide:

Step 1

Synthesis of 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylbenzoic acid.
Ethyl 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylphenyl carboxylate obtained in the same way as in Reference 18 was processed in the same way as in Reference Example 19, and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylbenzoic acid was obtained.
mp. 115°C (recrystallization solvent : chloroform-n-hexane),
NMR (400 MHz, DMSO-d6) δ ppm 1.85-2.40 (6H, m), 2.55 (3H, s), 3.69 (1H, m), 7.44 (1H, t), 7.48 (1H, s), 7.72 (1H, d), 7.80 (1H, d), 13.40 (1H, br).

(0322)

Step 2

Synthesis of N-(1H-tetrazol-5-yl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylbenzamide.
3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylbenzoic acid and 5-amino-1H-tetrazole were treated in the same way as in Example 88, and the title substance was obtained.
mp. 289°C (decomp) (recrystallization solvent : chloroform-ethanol),
IR v max cm-1 1646,
NMR (400 MHz, DMSO-d6) δ ppm 1.85-2.35 (6H, m), 2.57 (3H, s), 3.66 (1H, m), 7.44 (1H, t), 7.56 (1H, s), 7.69 (1H, d), 7.80 (1H, d), 12.52 (1H, br s),
MS(FAB)m/z 365 (M+ +1),
Elemental analysis values as C18H16N6OS;
Theoretical values (%) C, 59.32, H, 4.43, N, 23.06,
Measured values (%) C, 59.13, H, 4.48, N, 23.34.

(0323)

Example 95

N-(1H-tetrazol-5-yl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-fluorobenzamide:

Step 1

Synthesis of 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-fluorobenzoic acid.

Ethyl 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-fluorophenyl carboxylate obtained in the same way as in Reference Example 18 was processed in the same way as in Reference Example 19, and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-fluorobenzoic acid was obtained.

mp. 156°C (recrystallization solvent : chloroform-n-hexane),

NMR (400 MHz, DMSO-d6) δ ppm 1.82-2.35 (6H, m), 3.68 (1H, m), 7.53 (1H, t), 7.60 (1H, s), 8.09 (1H, m), 8.21 (1H, m), 13.39 (1H, br).

(0324)

Step 2

Synthesis of N-(1H-tetrazol-5-yl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-fluorobenzamide.

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-fluorobenzoic acid and 5-amino-1H-tetrazole were treated in the same way as in Example 88, and the title substance was obtained.

mp. 247-259°C (recrystallization solvent : chloroform-ethanol),

IR v max cm-1 1668,

NMR (400 MHz, DMSO-d6) δ ppm 1.85-2.40 (6H, m), 3.69 (1H, m), 7.63 (2H, m), 8.24 (1H, m), 8.50 (1H, m), 12.50 (1H, br),

MS(FAB)m/z 369 (M+ +1),

Elemental analysis values as C17H13FN6OS;

Theoretical values (%) C, 55.42, H, 3.56, N, 22.81,

Measured values (%) C, 55.47, H, 3.76,N, 23.17.

(0325)

Example 96

N-(1H-tetrazol-5-yl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methylbenzamide:

Step 1

Synthesis of 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methylbenzoic acid.

Ethyl 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methylphenyl carboxylate obtained in the same way as in Reference Example 18 was processed in the same way as in Reference Example 19, and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methylbenzoic acid was obtained.

mp. 163-165°C (decomp) (recrystallization solvent : chloroform-methanol),

NMR (400 MHz, CDCl3) δ ppm 1.90-2.00 (1H, m), 2.00-2.10 (1H, m), 2.20-2.50 (4H, m), 2.68 (3H, s), 3.70-3.80 (1H, m), 6.98 (1H, s), 7.29 (1H, d), 7.63 (1H, d), 8.31 (1H, s).

(0326)

Step 2

Synthesis of N-(1H-tetrazol-5-yl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methylbenzamide.

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methylbenzoic acid and 5-amino-1H-tetrazole were treated in the same way as in Example 88, and the title substance was obtained.

mp. 250-253°C (decomp) (recrystallization solvent : chloroform-methanol),

NMR (400 MHz, DMSO-d6) δ ppm 1.80-2.00 (1H, m), 2.00-2.10 (1H, m), 2.20-2.40 (4H, m), 2.55 (3H, s), 3.60-3.80 (1H, m), 7.49 (1H, d), 7.57 (1H, s), 7.77 (1H, d), 7.97 (1H, s), 8.02 (1H, br), 12.52 (1H, s),

MS(FAB)m/z 365 (M+ +1),

Elemental analysis values as C18H16N6OS•3/4H2O;

Theoretical values (%) C, 58.52,H, 4.52, N, 21.55,

Measured values (%) C, 58.75, H, 4.59, N, 21.35.

(0327)

Example 97

N-(1H-tetrazol-5-yl)-2-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide:

Step 1

Synthesis of 2-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzoic acid.

Ethyl 2-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl carboxylate obtained in the same way as in Reference Example 18 was processed in the same way as in Reference Example 19, and 2-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzoic acid was obtained.

mp. 142-145°C (decomp) (recrystallization solvent : chloroform-methanol),

NMR (400 MHz, DMSO-d6) δ ppm 1.80-1.90 (1H, m), 1.90-2.00 (1H, m), 2.20-2.50 (4H, m), 3.70-3.80 (1H, m), 7.08 (1H, s), 7.50-7.70 (4H, m), 12.50-12.70 (1H, br).

(0328)

Step 2

Synthesis of N-(1H-tetrazol-5-yl)-2-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide.

2-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzoic acid and 5-amino-1H-tetrazole were treated in the same way as in Example 88, and the title substance was obtained.

mp. 168-170°C (decomp) (recrystallization solvent : chloroform-methanol),

NMR (400 MHz, DMSO-d6) δ ppm 1.80-1.90 (1H, m), 1.90-2.00 (1H, m), 2.10-2.40 (4H, m), 3.60-3.80 (1H, m), 7.07 (1H, s), 7.50-7.70 (4H, m), 12.20 (1H, br),

MS(FAB)m/z 351 (M+ +1).

(0329)

Example 98

(E)-5-(2-(3-(2-[4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) ethenyl)-1H-tetrazole;

Step 1

Synthesis of (E)-5-(2-(3-iodo phenyl) ethenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

(E)-5-(2-(3-iodo phenyl) ethenyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and (E)-5-(2-(3-iodo phenyl) ethenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 115-116°C (recrystallization solvent : chloroform-n-hexane),

NMR (400 MHz, CDCl3) δ ppm 3.80 (3H, s), 5.69 (2H, s), 6.88-6.92 (2H, m), 7.10 (1H, d), 7.11 (1H, t), 7.34-7.37 (2H, m), 7.48 (1H, d), 7.59 (1H, d), 7.64 (1H, d), 7.88 (1H, s),

MS(EI)m/z 418(M+),

Elemental analysis values as C17H15IN4O;

Theoretical values (%) C, 48.82, H, 3.62,N, 13.40,

Measured values (%) C, 48.99, H, 3.72, N, 13.24.

(0330)

Step 2

Synthesis of (E)-5-(2-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl) ethenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

(E)-5-(2-(3-iodo phenyl) ethenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and (E)-5-(2-(3-(2-[4-cyclobutyl-2-thiazolyl] ethinyl) phenyl) ethenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as a pale oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.91-2.08 (2H, m), 2.30-2.30 (4H, m), 3.66-3.74 (1H, m), 3.80 (3H, s), 5.70 (2H, s), 6.89-6.92 (2H, m), 6.96 (1H, s), 7.14 (1H, d), 7.35-7.41 (3H, m), 7.53-7.56 (2H, m), 7.68 (1H, d), 7.75 (1H, s).

(0331)

Step 3

Synthesis of (E)-5-(2-(3-(2-[4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) ethenyl)-1H-tetrazole.

(E)-5-(2-(3-(2-[4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) ethenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 158-168°C (decomp) (recrystallization solvent : chloroform-n-hexane),

IR v max cm-1 2216, 1650, 1598, 1574, 1554, 1504,
NMR (400 MHz, DMSO-d6) δ ppm 1.86-2.03 (2H, m), 2.18-2.33 (4H, m), 3.63-3.71 (1H, m), 7.47 (1H, d), 7.53 (1H, s), 7.54 (1H, t), 7.63-7.67 (1H, m), 7.65 (1H, d), 7.83 (1H, d), 8.04 (1H, s),
MS(EI)m/z 333(M+),
Elemental analysis values as C18H15N5S;
Theoretical values (%) C, 64.84, H, 4.53, N, 21.01,
Measured values (%) C, 65.05, H, 4.60, N, 20.70.

(0332)

Example 99

(E)-5-(2-(3-(2-[4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1-propen-1-yl)-1H-tetrazole:

Step 1

Synthesis of (E)-5-(2-(3-iodo phenyl)-1-propen-1-yl)-2-(4-methoxybenzyl)-2H-tetrazole.

(E)-5-(2-(3-iodo phenyl)-1-propen-1-yl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and (E)-5-(2-(3-iodo phenyl)-1-propen-1-yl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as amorphous material.
NMR (400 MHz, CDCl3) δ ppm 2.66 (3H, d), 3.79 (3H, s), 5.72 (2H, s), 6.75-7.45 (8H, m), 7.88 (1H, s).

(0333)

Step 2

Synthesis of (E)-5-(2-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1-propen-1-yl)-2-(4-methoxybenzyl)-2H-tetrazole.

(E)-5-(2-(3-iodo phenyl)-1-propen-1-yl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and (E)-5-(2-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1-propen-1-yl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as brown oily substance.
NMR (400 MHz, CDCl3) δ ppm 1.85-2.44 (6H, m), 2.62 (3H, d), 3.70 (3H, s), 3.80 (3H, s), 5.72 (2H, s), 6.86-7.80 (10H, m).

(0334)

Step 3

Synthesis of (E)-5-(2-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1-propen-1-yl)-1H-tetrazole.

(E)-5-(2-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1-propen-1-yl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 134-135°C (recrystallization solvent = chloroform - n-hexane),
IR v max cm-1 2216,
NMR (400 MHz, DMSO-d6-CDCl3) δ ppm 1.85-2.42 (6H, m), 2.68 (3H, d), 3.69 (1H, m), 6.80 (1H, s), 7.15 (1H, s), 7.48 (1H, t), 7.58 (1H, d), 7.63 (1H, d), 7.78 (1H, m),
MS(FAB)m/z 348 (M+ +1),
Elemental analysis values as C19H17N5S • 1/4 H2O
Theoretical values (%) C, 64.84, H, 5.01, N, 19.90,
Measured values (%) C, 65.01, H, 5.06, N, 19.89..

(0335)

Example 100

(E)-5-(1-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1-propen-2-yl)-1H-tetrazole:

Step 1

Synthesis of (E)-5-(1-(3-iodo phenyl)-1-propen-2-yl)-2-(4-methoxybenzyl)-2H-tetrazole.

(E)-5-(21[3-iodo phenyl)-1-propen-2-yl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and (E)-5-(1-(3-iodo phenyl)-1-propen-2-yl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as amorphous material.
NMR (400 MHz, CDCl3) δ ppm 2.34 (3H, d), 3.80 (3H, s), 5.69 (2H, s), 6.90 (2H, d), 7.13 (1H, t), 7.47 (3H, m), 7.63 (2H, m), 7.76 (1H, s).

(0336)

Step 2

Synthesis of (E)-5-(1-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1-propen-2-yl)-2-(4-methoxybenzyl)-2H-tetrazole.

(E)-5-(1-(3-iodo phenyl)-1-propen-2-yl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and (E)-5-(1-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1-propen-2-yl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as brown oily substance.
NMR (400 MHz, CDCl3) δ ppm 1.85-2.40 (6H, m), 2.38 (3H, d), 3.70 (1H, s), 3.77 (3H, s), 5.70 (2H, s), 6.90 (2H, d), 6.95 (1H, s), 7.38 (2H, d), 7.43 (1H, m), 7.51 (1H, m), 7.64 (1H, br s), 7.71 (1H, br s).

(0337)

Step 3

Synthesis of (E)-5-(1-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1-propen-2-yl)-1H-tetrazole.

(E)-5-(1-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1-propen-2-yl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 134-136°C (recrystallization solvent = chloroform - n-hexane),
IR v max cm-1 2216,
NMR (400 MHz, CDCl3) δ ppm 1.85-2.40 (6H, m), 2.42 (3H, d), 3.78 (1H, m), 7.04 (1H, s), 7.35-7.45 (4H, m), 7.61 (1H, s), MS(EI)m/z 347(M+),
Elemental analysis values as C19H17N5S
Theoretical values (%) C, 65.68, H, 4.93, N, 20.16,
Measured values (%) C, 65.40, H, 5.05, N, 19.89..

(0338)

Example 101

(E)-5-(2-(4-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-thienyl)-2-ethenyl)-1H-tetrazole:

Step 1

Synthesis of (E)-5-(2-(4-bromo-2-thienyl)-2-ethenyl)-2-(4-methoxybenzyl)-2H-tetrazole.
(E)-5-(2-(4-bromo-2-thienyl)-2-ethenyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and (E)-5-(2-(4-bromo-2-thienyl)-2-ethenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.
mp. 83-84°C (recrystallization solvent = chloroform - n-hexane),
NMR (400 MHz, CDCl3) δ ppm 3.79 (3H, s), 5.67 (2H, s), 6.88-6.95 (2H, m), 7.07 (1H, s), 7.17 (1H, s), 7.34-7.36 (2H, m), 7.85 (1H, d).

(0339)

Step 2

Synthesis of (E)-5-(2-(4-iodo-2-thienyl)-2-ethenyl)-2-(4-methoxybenzyl)-2H-tetrazole.
(E)-5-(2-(4-bromo-2-thienyl)-2-ethenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 2 of Example 16, and (E)-5-(2-(4-iodo-2-thienyl)-2-ethenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.
mp. 103-104°C (recrystallization solvent = chloroform - n-hexane),
NMR (400 MHz, CDCl3) δ ppm 3.80 (3H, s), 5.68 (2H, s), 6.89-6.94 (2H, m), 7.13 (1H, s), 7.34-7.37 (3H, m), 7.73 (1H, d).

(0340)

Step 3

Synthesis of (E)-5-(2-(4-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-thienyl)-2-ethenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

(E)-5-(2-(4-iodo-2-thienyl)-2-ethenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and (E)-5-(2-(4-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-thienyl)-2-ethenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 133-135°C (recrystallization solvent = chloroform - n-hexane),

NMR (400 MHz, CDCl3) δ ppm 1.90-2.10 (2H, m), 2.28-2.38 (4H, m), 3.64-3.73 (1H, m), 3.80 (3H, s), 5.68 (2H, s), 6.89-6.92 (2H, m), 6.94 (1H, s), 6.95 (1H, d), 7.34-7.37 (2H, m), 7.56 (1H, s), 7.74 (1H, d).

(0341)

Step 4

Synthesis of (E)-5-(2-(4-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-thienyl)-2-ethenyl)-1H-tetrazole.

(E)-5-(2-(4-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-thienyl)-2-ethenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 156-163°C (decomp) (recrystallization solvent = chloroform - n-hexane),

IR v max cm-1 2216,

NMR (400 MHz, DMSO-d6) δ ppm 1.83-2.05 (2H, m), 2.18-2.32 (4H, m), 3.62-3.70 (1H, m), 7.12 (1H, d), 7.52 (1H, s), 7.74 (1H, s), 7.80 (1H, d), 8.21 (1H, s), MS(EI)m/z 339(M+),

Elemental analysis values as C16H13N5S2 • 1/4 H2O

Theoretical values (%) C, 55.87, H, 3.96, N, 20.36,

Measured values (%) C, 56.11, H, 3.92, N, 20.32..

(0342)

Example 102

(E)-5-(2-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-benzo (b) thienyl)-2-ethenyl)-1H-tetrazole:

Step 1

Synthesis of (E)-5-(2-(5-iodo-2-benzo (b) thienyl)-2-ethenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

(E)-5-(2-(5-iodo-2-benzo (b) thienyl)-2-ethenyl)-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and (E)-5-(2-(5-iodo-2-benzo (b) thienyl)-2-ethenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 144-146°C (recrystallization solvent = chloroform - n-hexane),

NMR (400 MHz, CDCl3) δ ppm 3.80 (3H, s), 5.69 (2H, s), 6.90 (2H, d), 7.00 (1H, d), 7.26 (1H, s), 7.36 (2H, d), 7.52 (1H, d), 7.59 (1H, d), 7.87 (1H, d), 8.08 (1H, s).

(0343)

Step 2

Synthesis of (E)-5-(2-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-benzo (b) thienyl)-2-ethenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

(E)-5-(2-(5-iodo-2-benzo (b) thienyl)-2-ethenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and (E)-5-(2-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-benzo (b) thienyl)-2-ethenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 145-148°C (recrystallization solvent = chloroform - n-hexane),

NMR (400 MHz, CDCl3) δ ppm 1.89-2.11 (2H, m), 2.30-2.41 (4H, m), 3.68-3.76 (1H, m), 3.80 (3H, s), 5.70 (2H, s), 6.89-6.92 (2H, m), 6.95 (1H, s), 7.02 (1H, d), 7.38-7.35 (3H, m), 7.52 (1H, d), 7.77 (1H, d), 7.89 (1H, d), 7.96 (1H, s).

(0344)

Step 3

Synthesis of (E)-5-(2-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-benzo (b) thienyl)-2-ethenyl)-1H-tetrazole.

(E)-5-(2-(5-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-benzo (b) thienyl)-2-ethenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 222-224°C (decomp) (recrystallization solvent = chloroform-ethanol-n-hexane),

IR v max cm-1 2216, 1638,

NMR (400 MHz, DMSO-d6) δ ppm 1.86-2.03 (2H, m), 2.21-2.31 (4H, m), 3.63-3.72 (1H, m), 7.11 (1H, d), 7.53 (1H, s), 7.64 (1H, d), 7.82 (1H, s), 7.98 (1H, d), 8.12 (1H, d), 8.20 (1H, s),

MS(FAB)m/z 390 (M+ +1),

Elemental analysis values as C20H15N5 S2

Theoretical values (%) C, 61.67,H, 3.88, N, 17.98,

Measured values (%) C, 61.97, H, 3.99, N, 17.61..

(0345)

Example 103

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole-5-carboxamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole-5-carboxamide.

Methylene chloride 10 ml were added to 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl aniline 509 mg, carboxylic acid 1.14 g of Reference Example 19, 1-ethyl-1'-(3-dimethylamino) propyl carbodiimide hydrochloride 1.04 g and 4-dimethylaminopyridine 598 mg, and the mixture was stirred at room temperature for 15 hours. The reaction liquor was diluted with chloroform 100 ml and was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution and thereafter, was dried with sodium sulfate. The residue obtained by distilling off the solvent was purified by column chromatography (eluate = n-hexane : ethyl acetate = 3 : 2) using silica gel, and the obtained crude crystals were recrystallised from chloroform-ether, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole-5-carboxamide 1 g was obtained as a pale yellow needle crystal.
mp. 114-115°C,
NMR (400 MHz, CDCl3) δ ppm 1.88-2.11 (2H, m), 2.27-2.41 (4H, m), 3.72 (1H, m), 3.80 (3H, s), 5.79 (2H, s), 6.90 (2H, d), 6.96 (1H, s), 7.37-7.42 (4H, m), 7.77 (1H, ddd), 7.78 (1H, s), 8.06 (1H, s),
Elemental analysis values as C25H22N6O2S
Theoretical values (%) C, 63.81, H, 4.71, N, 17.86,
Measured values (%) C, 63.73, H, 4.84, N, 17.78..

(0346)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole-5-carboxamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole-5-carboxamide was treated in the same way as in Step 3 of Example 1, and the title substance was obtained.
mp. 214-215°C (decomp) (recrystallization solvent = chloroform-ethanol-n-hexane),
IR v max cm-1 2216, 1660,
NMR (400 MHz, DMSO-d6) δ ppm 1.85-2.06 (2H, m), 2.20-2.51 (4H, m), 3.68 (1H, m), 7.44-7.52 (3H, m), 7.95 (1H, d), 8.16 (1H, s),
Elemental analysis values as C17H14N6OS
Theoretical values (%) C, 58.27,H, 4.03, N, 23.98,
Measured values (%) C, 58.15, H, 4.25, N, 23.55..

(0347)

Example 104

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylphenyl)-1H-tetrazole-5-carboxamide:

Step 1

Synthesis of 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylaniline.

3-iodo-2-methyl nitrobenzene and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Reference Example 16, and continuing, it was treated in the same way as in Reference Example 17, and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylaniline was obtained as a pale-brown oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.91-2.40 (9H, m), 3.70 (1H, m), 6.71 (1H, dd), 6.94 (1H, s), 6.99-7.05 (2H, m).

(0348)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole-5-carboxamide.

Toluene 5 ml and catalytic quantity of DMF were added to thionyl chloride 0.5 ml and carboxylic acid 1.26 g of Reference Example 19, and the mixture was heated under reflux for three hours. After cooling, the reaction liquor was eliminated by distillation. The residue was dissolved in methylene chloride 20 ml, and this was added under stirring at 0°C to 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylaniline 966 mg and triethylamine 0.8ml of methylene chloride 20 ml solution. On completion of the dropwise addition, the reaction liquor was stirred at room temperature for two hours. The reaction liquor was discharged into 1N hydrochloric acid 50 ml and extraction was carried out with chloroform. The extract layer was washed with saturated sodium bicarbonate and thereafter, was dried with sodium sulfate. The residue obtained by elimination by distillation of the solvent was purified by column chromatography (eluate = chloroform = methanol = 100 : 1) using silica gel, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole-5-carboxamide 1.95 g were obtained as a brown oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.92-2.08 (2H, m), 2.28-2.40 (4H, m), 2.56 (3H, s), 3.66-3.72 (1H, m), 3.80 (3H, s), 5.80 (2H, s), 6.90 (2H, d), 6.97 (1H, s), 7.27 (1H, t), 7.42 (2H, d), 7.46 (1H, d), 8.11 (1H, d), 8.82 (1H, s).

(0349)

Step 3

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylphenyl)-1H-tetrazole-5-carboxamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole-5-carboxamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 190-191°C (decomp) (recrystallization solvent = chloroform - ethanol - n-hexane),

IR v max cm-1 2208, 1700, 1672, 1600, 1542, 1504,
NMR (400 MHz, DMSO-d6) δ ppm 1.88-2.03 (2H, m), 2.19-2.31 (4H, m), 2.42 (3H, s), 3.63-3.72 (1H, m), 7.36 (1H, t), 7.51-7.54 (1H, m), 7.54 (1H, s), 7.60 (1H, d), 10.96 (1H, s),
MS(FAB)m/z 365 (M+ +1),
Elemental analysis values as C18H16N6OS
Theoretical values (%) C, 59.32, H, 4.43, N, 23.07,
Measured values (%) C, 59.28, H, 4.34, N, 23.26..

(0350)

Example 105

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methylphenyl)-1H-tetrazole-5-carboxamide:

Step 1

Synthesis of 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methylaniline.

3-iodo-6-methyl nitrobenzene and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Reference Example 16, and continuing, it was treated in the same way as in Reference Example 17, and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methylaniline was obtained.
mp. 125-126°C (recrystallization solvent = chloroform - n-hexane),
IR v max cm-1 3460, 3348, 2980, 2940, 2200, 1624, 1566,
NMR (400 MHz, CDCl3) δ ppm 1.90-2.07 (2H, m), 2.17 (3H, s), 2.28-2.38 (4H, m), 3.63-3.70 (1H, m), 6.88 (1H, d), 6.91 (1H, s), 6.94 (1H, dd), 7.03 (1H, d),
MS(FAB)m/z 269 (M+ +1),
Elemental analysis values as C16H16N2S
Theoretical values (%) C, 71.60, H, 6.01, N, 10.44,
Measured values (%) C, 71.32, H, 5.85, N, 10.37..

(0351)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole-5-carboxamide.

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methylaniline and carboxylic acid of Reference Example 19 was processed in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole-5-carboxamide was obtained.
mp. 138-140°C (recrystallization solvent = chloroform - n-hexane),
IR v max cm-1 3408, 2212, 1704, 1614,

NMR (400 MHz, CDCl3) δ ppm 1.93-2.07 (2H, m), 2.29-2.36 (4H, m), 2.39 (3H, s), 3.66-3.71 (1H, m), 3.80 (3H, s), 5.80 (2H, s), 6.89-6.91 (2H, m), 6.94 (1H, s), 7.23 (1H, d), 7.35 (1H, d), 7.40-7.42 (2H, m), 8.32 (1H, s), 8.78 (1H, s),
MS(FAB)m/z 485 (M+ +1),
Elemental analysis values as C26H24N6 O2 S
Theoretical values (%) C, 64.44, H, 4.99, N, 17.35,
Measured values (%) C, 64.22, H, 5.14, N, 17.64..

(0352)

Step 3

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methylphenyl)-1H-tetrazole-5-carboxamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methylphenyl)-2-(4-methoxybenzyl)-2H-tetrazole-5-carboxamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 214-215°C (decomp) (recrystallization solvent = chloroform-ethanol-n-hexane),
IR v max cm-1 3412, 3092, 2204, 1710, 1570,
NMR (400 MHz, DMSO-d6) δ ppm 1.85-2.02 (2H, m), 2.20-2.31 (4H, m), 2.50 (3H, s), 3.64-3.70 (1H, m), 7.41 (1H, d), 7.50-7.51 (1H, m), 7.54 (1H, s), 7.68 (1H, s), 10.84 (1H, s),
MS(FAB)m/z 365 (M+ +1),
Elemental analysis values as C18H16N6OS • 1/4 H2O
Theoretical values (%) C, 58.60, H, 4.51, N, 22.78,
Measured values (%) C, 58.76, H, 4.53, N, 23.16..

(0353)

Example 106

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methoxyphenyl)-1H-tetrazole-5-carboxamide:

Step 1

Synthesis of 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methoxyaniline.

3-iodo-2-methoxy nitrobenzene and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Reference Example 16, and continuing, it was treated in the same way as in Reference Example 17, and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methoxyaniline was obtained as a pale yellow oily substance.
NMR (400 MHz, CDCl3) δ ppm 1.90-2.07 (2H, m), 2.28-2.39 (4H, m), 3.65-3.74 (1H, m), 4.00 (3H, s), 6.77 (1H, d), 6.88 (1H, t), 6.92-6.94 (2H, m).

(0354)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole-5-carboxamide.

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methoxyaniline and carboxylic acid of Reference Example 19 was processed in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole-5-carboxamide was obtained.

mp. 137-138°C,

IR v max cm-1 3384, 3100, 2212, 1704, 1606,

NMR (400 MHz, CDCl3) δ ppm 1.91-2.09 (2H, m), 2.29-2.40 (4H, m), 3.68-3.73 (1H, m), 3.80 (3H, s), 4.17 (3H, s), 5.80 (2H, s), 6.90 (2H, d), 6.99 (1H, s), 7.13 (1H, t), 7.34 (1H, d), 7.42 (2H, d), 8.58 (1H, d), 9.56 (1H, s),

MS(FAB)m/z 501 (M+ +1),

Elemental analysis values as C26H24N6O3 S • 1/4 H2O

Theoretical values (%) C, 61.83, H, 4.89,N, 16.64,

Measured values (%) C, 61.96, H, 4.87, N, 16.19..

(0355)

Step 3

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methoxymethyl phenyl)-1H-tetrazole-5-carboxamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole-5-carboxamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 220-221°C (decomp) (recrystallization solvent = chloroform-ethanol-n-hexane),

IR v max cm-1 3384, 3090, 2212, 1606,

NMR (400 MHz, DMSO-d6) δ ppm 1.86-2.03 (2H, m), 2.21-2.33 (4H, m), 3.64-3.72 (1H, m), 4.03 (3H, s), 7.27 (1H, t), 7.53 (1H, d), 7.56 (1H, d), 8.02 (1H, d), 10.32 (1H, s), MS(EI)m/z 380(M+),

Elemental analysis values as C18H16N6 O2 S

Theoretical values (%) C, 56.82, H, 4.24, N, 22.10,

Measured values (%) C, 56.63, H, 4.38, N, 21.73..

(0356)

Example 107

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methoxyphenyl)-1H-tetrazole-5-carboxamide:

Step 1

Synthesis of 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methoxyaniline.

3-iodo-6-methoxy nitrobenzene and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Reference Example 16, and continuing, it was treated in the same way as in Reference Example 17, and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methoxyaniline was obtained as a pale yellow oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.89-2.07 (2H, m), 2.28-2.38 (4H, m), 3.63-3.72 (1H, m), 3.87 (3H, s), 6.75 (1H, d), 6.89 (1H, s), 6.92 (1H, d), 7.01 (1H, dd).

(0357)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole-5-carboxamide.

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methoxyaniline and carboxylic acid of Reference Example 19 was processed in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole-5-carboxamide was obtained.

mp. 158-160°C,

IR v max cm-1 3384, 2212, 1698, 1612, 1550, 1510,

NMR (400 MHz, CDCl3) δ ppm 1.91-2.07 (2H, m), 2.29-2.38 (4H, m), 3.64-3.73 (1H, m), 3.80 (3H, s), 3.98 (3H, s), 5.80 (2H, s), 6.89-6.92 (4H, m), 7.38 (1H, dd), 7.41 (1H, d), 8.75 (1H, d), 9.46 (1H, s), MS(EI)m/z 500(M+),

Elemental analysis values as C26H24N6O3S

Theoretical values (%) C, 62.38, H, 4.83, N, 16.79,

Measured values (%) C, 62.15, H, 4.93, N, 16.75..

(0358)

Step 3

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methoxymethyl phenyl)-1H-tetrazole-5-carboxamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methoxyphenyl)-2-(4-methoxybenzyl)-2H-tetrazole-5-carboxamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. >300°C (recrystallization solvent = chloroform - n-hexane),

NMR (400 MHz, DMSO-d6) δ ppm 1.89-2.02 (2H, m), 2.22-2.29 (4H, m), 3.64-3.68 (1H, m), 4.00 (3H, s), 7.20 (1H, d), 7.40 (1H, d), 7.48 (1H, d), 8.63 (1H, s), 9.63 (1H, s),

Elemental analysis values as C18H16N6O2S
Theoretical values (%) C, 56.82, H, 4.24, N, 22.10,
Measured values (%) C, 56.63, H, 4.38, N, 21.73..

(0359)

Example 108

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-(ethoxycarbonylmethyl)-1H-tetrazole-5-carboxamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) glycine ethyl ester.

DMF 5 ml were added to 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl aniline 301 mg, potassium carbonate 204 mg and bromine ethyl acetate ester 0.145 ml, and the mixture was stirred at room temperature for 24 hours. The reaction liquor was diluted with ethyl acetate 300 ml and was washed with saturated aqueous sodium chloride solution, and thereafter, drying with magnesium sulfate was carried out. The residue obtained by elimination by distillation of the solvent was purified by column chromatography (eluate = n-hexane : ethyl acetate = 2 : 1) using silica gel, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) glycine ethyl ester 214 mg was obtained.
mp. 110-112°C,
NMR (400 MHz, CDCl3) δ ppm 1.31 (3H, t), 1.88-2.10 (2H, m), 2.27-2.42 (4H, m), 3.69 (1H, m), 3.90 (2H, d), 4.26 (2H, q), 4.37 (1H, t), 6.64-6.67 (1H, m), 6.80 (1H, t), 6.93 (1H, s), 6.99 (1H, d), 7.17 (1H, t).

(0360)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-(ethoxycarbonylmethyl)-2-(4-methoxybenzyl)-2H-tetrazole-5-carboxamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) glycine ethyl ester and carboxylic acid of Reference Example 19 were treated in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-(ethoxycarbonylmethyl)-2-(4-methoxybenzyl)-2H-tetrazole-5-carboxamide was obtained as a pale yellow oily substance.
NMR (400 MHz, CDCl3) δ ppm 1.29 (3H, t), 1.91-2.08 (2H, m), 2.28-2.39 (4H, m), 3.65-3.73 (1H, m), 3.75 (3H, s), 4.24 (2H, q), 4.58 (2H, s), 5.54 (2H, s), 6.82 (1H, d), 6.97 (1H, s), 7.10 (1H, d), 7.19-7.23 (2H, m), 7.43-7.45 (1H, m), 7.48 (1H, s).

(0361)

Step 3

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-(ethoxycarbonylmethyl)-1H-tetrazole-5-carboxamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-(ethoxycarbonylmethyl)-2-(4-methoxybenzyl)-2H-tetrazole-5-carboxamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 184-186°C (decomp),

IR v max cm-1 3408, 2216, 1744, 1624,

NMR (400 MHz, DMSO-d6) δ ppm 1.18 (3H, t), 1.85-2.04 (2H, m), 2.18-2.30 (4H, m), 3.62-3.70 (1H, m), 4.13 (2H, q), 4.71 (2H, br s), 7.27-7.45 (4H, m), 7.51 (1H, s),

MS(FAB)m/z 437 (M+ +1),

Elemental analysis values as C21H20N6O3S

Theoretical values (%) C, 57.78, H, 4.62, N, 19.26,

Measured values (%) C, 57.46,H, 4.62, N, 19.74..

(0362)

Example 109

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-methyl-1H-tetrazole-5-carboxamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) trifluoro acetamide.

Methylene chloride 10 ml were added to 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline 209 mg and triethylamine 1 ml, and trifluoroacetic anhydride 0.126 ml under ice cooled stirring were added. The reaction liquor is stirred at room temperature for 15 hours, and thereafter, 1N hydrochloric acid 100 ml is added. Extraction was carried out with hydrochloric acid methylene. The liquid extract was washed with saturated aqueous sodium chloride solution and thereafter, was dried with sodium sulfate. The residue obtained by elimination by distillation of the solvent was purified by column chromatography (eluate = n-hexane : ethyl acetate = 5 : 1) using silica gel, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) trifluoro acetamide 198 mg was obtained as an oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.99-2.09 (2H, m), 2.27-2.42 (4H, m), 3.70 (1H, m), 6.98 (1H, s), 7.41 (1H, t), 7.47 (1H, dt), 7.61 (1H, d), 7.81 (1H, t), 7.93 (1H, br s).

(0363)

Step 2

Synthesis of N-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-N-methylaniline.

DMF 5 ml were added to (3-(2-(4-cyclobutyl-2-thiazolyl), ethinyl) phenyl) trifluoro acetamide 198 mg, potassium carbonate 117 mg and methyl iodide 0.04 ml, and the mixture was stirred at

room temperature for eight hours. 1N hydrochloric acid 10 ml and water 100 ml were added to the reaction liquor and were extracted with ethyl acetate. The liquid extract was washed with saturated aqueous sodium chloride solution and thereafter, was dried with sodium sulfate. Sodium carbonate 120 mg, water 5 ml and methanol 15 ml were added to the residue obtained by elimination by distillation of the solvent, and the mixture was stirred at room temperature for eight hours. The reaction liquor was diluted with ethyl acetate 100 ml and was washed with saturated aqueous sodium chloride solution and thereafter, was dried with sodium sulfate. the solvent was eliminated by distillation, and N-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-N-methylaniline 130 mg was obtained as yellow needle crystal.
mp. 73-75°C,
NMR (400 MHz, CDCl3) δ ppm 1.87-2.10 (2H, m), 2.26-2.40 (4H, m), 2.83 (3H, s), 3.69 (1H, m), 6.63 (1H, d), 6.80 (1H, t), 6.92 (1H, s), 6.93 (1H, d), 7.16 (1H, t).

(0364)

Step 3

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-methyl-2-(4-methoxybenzyl)-2H-tetrazole-5-carboxamide.

N-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-N-methylaniline and carboxylic acid of Reference Example 21 were treated in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-methyl-2-(4-methoxybenzyl)-2H-tetrazole-5-carboxamide was obtained as a pale yellow oily substance.
NMR (400 MHz, CDCl3) δ ppm 1.91-2.09 (2H, m), 2.28-2.39 (4H, m), 3.50 (3H, s), 3.65-3.73 (1H, m), 3.75 (3H, s), 5.54 (2H, s), 6.82 (2H, d), 6.97 (1H, s), 7.08-7.10 (3H, m), 7.20-7.21 (1H, m), 7.34 (1H, s), 7.42 (1H, d).

(0365)

Step 4

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-methyl-1H-tetrazole-5-carboxamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-methyl-2-(4-methoxybenzyl)-2H-tetrazole-5-carboxamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 229-230°C (decomp),
IR v max cm-1 3404, 2216, 1618,
NMR (400 MHz, DMSO-d6) δ ppm 1.86-2.01 (2H, m), 2.17-2.30 (4H, m), 3.42 (3H, s), 3.61-3.70 (1H, m), 7.23 (1H, d), 7.34 (1H, t), 7.43 (1H, d), 7.46 (1H, s), 7.51 (1H, s), MS(FAB). m/z 365 (M+ +1),

Elemental analysis values as C18H16N6OS
Theoretical values (%) C, 59.32, H, 4.43, N, 23.07,
Measured values (%) C, 58.89, H, 4.27, N, 22.78..

(0366)

Example 110

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1H-(1, 2,3) triazole:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) propiol amide.

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline and propiolic acid were processed in the same way as in Step 1 of Example 103, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) propiol amide was obtained.
mp. 158-160°C (recrystallization solvent = chloroform-ether),
NMR (400 MHz, CDCl3) δ ppm 1.88-2.10 (2H, m), 2.27-2.42 (4H, m), 2.99 (1H, s), 3.70 (1H, m), 6.97 (1H, s), 7.34 (1H, t), 7.36 (1H, dd), 7.59 (1H, dd), 7.75 (1H, s), 7.77 (1H, br s).

(0367)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1H-(1, 2,3) triazole.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) propiol amide was treated in the same way as in Step 1 of Example 77, and the title substance was obtained.
mp. 259-262°C (recrystallization solvent = ethanol-ether),
NMR (400 MHz, DMSO-d6) δ ppm 1.87-2.05 (2H, m), 2.19-2.31 (4H, m), 3.67 (1H, m), 7.38 (1H, d), 7.46 (1H, t), 7.53 (1H, s), 7.92 (1H, d), 8.16 (1H, s), 8.59 (1H, brs), 10.62 (1H, s),
MS(EI)m/z 341(M+),
Elemental analysis values as C18H15N5OS • 1/2 H2O
Theoretical values (%) C, 60.32, H, 4.50, N, 19.54,
Measured values (%) C, 60.58,H, 4.31, N, 19.16..

(0368)

Example 111

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) maleamidic acid :

Toluene 5ml and THF 2ml were added to 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline 274 mg and maleic anhydride 106 mg, and the mixture was heated under reflux for two hours. This was cooled, thereby obtained crystals were recovered, and it was recrystallised from chloroform - ethanol - n-hexane, and the title substance was obtained as yellow fine needle crystal.

mp. 170-172°C (decomp),
IR v max cm-1 3412, 2216, 1708, 1628,
NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.09 (2H, m), 2.19-2.33 (4H, m), 3.67 (1H, m), 6.32 (1H, d), 6.50 (1H, d), 7.37 (1H, d), 7.44 (1H, t), 7.53 (1H, s), 7.63 (1H, d), 7.98 (1H, s), 10.53 (1H, s), 12.96 (1H, s), MS(EI)m/z 353(M+).

(0369)

Example 112

2-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) aminocarbonyl-1-cyclohexene-1-carboxylic acid :

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline and 3, 4, 5, 6-tetrahydrophthalic anhydride were treated in the same way as in Example 111, and the title substance was obtained.
mp. 139-141°C (recrystallization solvent = chloroform - n-hexane),
IR v max cm-1 3300, 2944, 2216, 1718, 1662, 1640, 1606,
NMR (400 MHz, DMSO-d6) δ ppm 1.63 (4H, s), 1.83-2.08 (2H, m), 2.20-2.33 (8H, m), 3.62-3.70 (1H, m), 7.31 (1H, d), 7.39 (1H, d), 7.52 (1H, s), 7.59 (1H, d), 7.96 (1H, s), 10.17 (1H, s), 12.46 (1H, br s),
MS(FAB)m/z 407 (M+ +1),
Elemental analysis values as C23H22N2O3 S • 1/4 H2O
Theoretical values (%) C, 67.21, H, 5.52, N, 6.82,
Measured values (%) C, 67.15, H, 5.40, N, 6.89..

(0370)

Example 113

2-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) aminocarbonyl-1-cyclopropanecarboxylic acid:

Step 1

Synthesis of methyl 2-(N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) aminocarbonyl)-1-cyclopropane carboxylate.

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline and 2-methoxycarbonyl-1-cyclopropanecarboxylic acid were processed in the same way as in Step 1 of Example 103, and methyl 2-(N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) aminocarbonyl)-1-cyclopropane carboxylate was obtained as a straw-coloured oily substance.
NMR (400 MHz, CDCl3) δ ppm 1.42-1.45 (1H, m), 1.70-1.80 (1H, m), 1.91-2.09 (4H, m), 2.11-2.38 (4H, m), 3.69 (1H, m), 3.75 (3H, s), 6.95 (1H, s), 7.27-7.30 (2H, m), 7.60 (1H, d), 7.72 (1H, s), 8.56 (1H, s).

(0371)

Step 2

Synthesis of 2-(N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) aminocarbonyl)-1-cyclopropanecarboxylic acid.

Methyl 2-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) aminocarbonyl-1-cyclopropane carboxylate was processed in the same way as in Example 56, and the title substance was obtained.

mp. 177-178°C (recrystallization solvent = ethanol - ether),

NMR (400 MHz, DMSO-d6) δ ppm 1.18-1.23 (1H, m), 1.58-1.62 (1H, m), 1.87-2.09 (3H, m), 2.19-2.38 (5H, m), 3.65 (1H, m), 7.20 (1H, s), 7.25 (1H, t), 7.32 (1H, d), 7.58 (1H, d), 7.98 (1H, s), 10.20 (1H, s), 12.06 (1H, s),

Elemental analysis values as C20H18N2 O3 S • 1/4 H2O

Theoretical values (%) C, 64.76, H, 5.03, N, 7.55,

Measured values (%) C, 64.92, H, 5.01, N, 7.53..

(0372)

Example 114

2-N-((3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) amino) carbonyl-1-cyclopentene-1-carboxylic acid :

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline and 1-cyclopentene-1,2-dicarboxylic acid anhydride were treated in the same way as in Example 111, and the title substance was obtained.

mp. 170-172°C (recrystallization solvent = chloroform - n-hexane),

IR v max cm-1 3320, 2948, 2216, 1698, 1590,

NMR (400 MHz, DMSO-d6) δ ppm 1.63 (4H, s), 1.85-2.02 (4H, m), 2.20-2.30 (4H, m), 2.63-2.65 (2H, m), 2.76-2.77 (2H, m), 3.62-3.70 (1H, m), 7.36 (1H, d), 7.42 (1H, t), 7.53 (1H, s), 7.64 (1H, d), 7.97 (1H, s), 10.41 (1H, s), 12.69 (1H, brs),

Elemental analysis values as C22H20N2O3 S • 1/4 H2O

Theoretical values (%) C, 66.56, H, 5.20, N, 7.06,

Measured values (%) C, 66.47,H, 4.98, N, 7.41..

(0373)

Example 115

(cis)-2-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) aminocarbonyl-4-cyclohexene-1-carboxylic acid :

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline and (cis)-4-cyclohexene-1,2-dicarboxylic acid anhydride were treated in the same way as in Example 111, and the title substance was obtained.

mp. 176-179°C (recrystallization solvent = chloroform-ethanol-n-hexane),
IR v max cm-1 3320, 2940, 2216, 1710, 1688,
NMR (400 MHz, DMSO-d6) δ ppm 1.86-2.02 (2H, m), 2.18-2.23 (4H, m), 2.25-2.62 (6H, m), 2.90-2.91 (1H, m), 3.04-3.05 (1H, m), 3.61-3.70 (1H, m), 7.29 (1H, d), 7.38 (1H, t), 7.51 (1H, s), 7.57 (1H, d), 7.95 (1H, s), 9.92 (1H, s), 12.13 (1H, s),
MS(FAB)m/z 407 (M+ +1),
Elemental analysis values as C23H22N2 O3 S • 1/4 H2O
Theoretical values (%) C, 67.21,H, 5.52, N, 6.82,
Measured values (%) C, 67.26, H, 5.41, N, 6.81..

(0374)

Example 116

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-methyl maleamidic acid :

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline and methyl maleic acid anhydride were treated in the same way as in Example 111, and the title substance was obtained.
mp. 132-136°C (decomp),
IR v max cm-1 2216, 1706, 1632,
NMR (400 MHz, DMSO-d6) δ ppm 1.83-2.09 (2H, m), 2.00 (3H, d), 2.16-2.34 (4H, m), 3.67 (1H, m), 6.11 (1H, d), 7.33 (1H, d), 7.42 (1H, t), 7.53 (1H, s), 7.62 (1H, d), 7.97 (1H, s), 10.33 (1H, s), 12.85 (1H, s),
MS(FAB)m/z 367 (M+ +1),
Elemental analysis values as C20H18N2 O3 S • H2O
Theoretical values (%) C, 62.48, H, 5.24, N, 7.29,
Measured values (%) C, 62.77, H, 4.88, N, 7.28..

(0375)

Example 117

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-phenyl maleamidic acid :

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline and phenyl maleic anhydride were processed in the same way as in Example 111, and the title substance was obtained.
mp. 172-175°C (decomp),
IR v max cm-1 2212, 1712, 1686,
NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.05 (2H, m), 2.19-2.33 (4H, m), 3.67 (1H, m), 6.61 (1H, d), 7.37 (1H, d), 7.44-7.55 (7H, m), 7.65 (1H, s), 8.04 (1H, s), 10.54 (1H, s), 13.20-13.23 (1H, br),
MS(FAB)m/z 429 (M+ +1),
Elemental analysis values as C25H20N2 O3 S

Theoretical values (%) C, 70.07, H, 4.70, N, 6.54,
Measured values (%) C, 69.70, H, 4.86, N, 6.43..

(0376)

Example 118

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2,3-dichloro maleamidic acid :

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline and 2, 3-dichloro maleic anhydride were processed in the same way as in Example 111, and the title substance was obtained.
mp. 153-156°C (decomp),
IR v max cm-1 2212, 1724, 1678, 1608, 1586,
NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.05 (2H, m), 2.18-2.33 (4H, m), 3.67 (1H, m), 7.42 (1H, d), 7.47 (1H, t), 7.54 (1H, s), 7.59 (1H, d), 7.90 (1H, s), 10.96 (1H, s),
MS(FAB)m/z 421(M+),
Elemental analysis values as C19H14Cl2 N2 O3 S
Theoretical values (%) C, 54.17, H, 3.35, N, 6.65,
Measured values (%) C, 54.01, H, 3.52, N, 6.43..

(0377)

Example 119

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2,3-dibromo maleamidic acid :

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline and 2, 3-dibromo maleic anhydride were processed in the same way as in Example 111, and the title substance was obtained.
mp. 119-120°C (decomp),
IR v max cm-1 2212, 1674, 1608, 1584,
NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.05 (2H, m), 2.18-2.33 (4H, m), 3.67 (1H, m), 7.41 (1H, d), 7.46 (1H, t), 7.54 (1H, s), 7.59 (1H, d), 7.89 (1H, s), 10.86 (1H, s),
MS(FAB)m/z 513 is) (509(M+) +1), 511.
Elemental analysis values as C19H14Br2 N2 O3 S
Theoretical values (%) C, 44.73, H, 2.77, N, 5.49,
Measured values (%) C, 44.92, H, 3.13, N, 5.39..

(0378)

Example 120

4-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) aminocarbonyl-3-carboxy-3-butenoic acid :

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline and (cis)-aconitine acid anhydride were treated in the same way as in Example 111, and the title substance was obtained.
mp. 131-132°C (decomp) (recrystallization solvent = chloroform - n-hexane),

IR v max cm-1 2212, 1718, 1634, 1582, 1550,
NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.05 (2H, m), 2.19-2.33 (4H, m), 3.32 (2H, s), 3.67 (1H, m), 6.46 (1H, s), 7.36-7.33 (1H, m), 7.43 (1H, t), 7.53 (1H, s), 7.63 (1H, d), 7.97 (1H, s), 10.47 (1H, s), 12.59 (1H, br), 12.96 (1H, br),
MS(FAB)m/z 411 (M+ +1),
Elemental analysis values as C21H18N2O5 S • 1/2 H2O
Theoretical values (%) C, 60.13, H, 4.57, N, 6.68,
Measured values (%) C, 60.44, H, 4.55, N, 6.62..

(0379)

Example 121

(cis)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1,2-cyclohexane amide acid :
3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline and (cis)-1,2-cyclohexanedicarboxylic acid anhydride were treated in the same way as in Example 111, and the title substance was obtained.
mp. 179-180°C (recrystallization solvent = chloroform-ethanol-n-hexane),
IR v max cm-1 2216, 1706, 1606, 1584, 1544,
NMR (400 MHz, DMSO-d6) δ ppm 1.31-2.31 (14H, m), 2.60-2.61 (1H, m), 2.94-2.95 (1H, m), 3.62-3.70 (1H, m), 7.29 (1H, d), 7.38 (1H, t), 7.51 (1H, s), 7.56 (1H, d), 7.97 (1H, s), 9.91 (1H, s), 11.95 (1H, br s),
MS(FAB)m/z 409 (M+ +1),
Elemental analysis values as C23H24N2 O3 S • 1/4 H2O
Theoretical values (%) C, 66.89, H, 5.98, N, 6.78,
Measured values (%) C, 66.95, H, 5.95, N, 6.75..

(0380)

Example 122

(trans).-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1,2-cyclohexane amide acid :
3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline and (trans)-1,2-cyclohexanedicarboxylic acid anhydride were treated in the same way as in Example 111, and the title substance was obtained.
mp. 200-201°C (recrystallization solvent = chloroform),
IR v max cm-1 2216, 1726, 1666, 1644, 1608, 1582, 1500,
NMR (400 MHz, DMSO-d6) δ ppm 1.85-2.55 (16H, m), 3.62-3.70 (1H, m), 7.29 (1H, d), 7.38 (1H, t), 7.51 (1H, s), 7.58 (1H, d), 7.96 (1H, s), 10.13 (1H, s), 12.08 (1H, s),
MS(FAB)m/z 409 (M+ +1),
Elemental analysis values as C23H24N2 O3 S
Theoretical values (%) C, 67.62, H, 5.92, N, 6.86,
Measured values (%) C, 67.51, H, 5.86, N, 6.83..

(0381)

Example 123

N-(3-(2-[2-benzothiazole) ethinyl) phenyl) maleamidic acid :

3-(2-(2-benzothiazole) ethinyl) aniline and maleic anhydride were treated in the same way as in Example 111, and the title substance was obtained.

mp. 169-171°C (recrystallization solvent : chloroform - ethanol),

IR v max cm-1 2212, 1702, 1628, 1554,

NMR (400 MHz, CDCl3) δ ppm 6.33 (1H, d), 6.50 (1H, d), 7.44-7.50 (2H, m), 7.68 (1H, d), 8.05-8.10 (2H, m), 8.18 (1H, s), 10.57 (1H, s), 12.95 (1H, s),

MS(FAB)m/z 349 (M+ +1).

(0382)

Example 124

(Z)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(1H-tetrazol-5-yl) cinnamide:

Step 1

Synthesis of 2-(4-methoxybenzyl)-2H-tetrazole-5-carbaldehyde.

Carboxylic acid 16 g of Reference Example 19 was dissolved in ethanol 100 ml, and sodium borohydride 3.57 g under stirring was gradually added at 0°C. The reaction liquor was stirred at room temperature for 12 hours, and thereafter, iced water 100 ml were added, and oxalic acid was added, and it was neutralized. This was extracted with methylene chloride, and the extract was washed with saturated aqueous sodium chloride solution, and thereafter, drying with magnesium sulfate was carried out. Toluene 100 ml and active manganese dioxide 15.3 g were added to an oily substance obtained by elimination by distillation of the solvent without being purified, and the mixture was heated under reflux for three hours. After cooling, the solvent was eliminated by distillation, and the residue was purified by column chromatography (eluate = n-hexane : ethyl acetate = 4 : 1) using silica gel, and 2-(4-methoxybenzyl)-2H-tetrazole-5-carbaldehyde 4.5 g were obtained as a straw-coloured oily substance.

IR v max cm-1 1726,

NMR (400 MHz, CDCl3) δ ppm 3.80 (3H, s), 5.79 (2H, s), 6.91 (2H, dt), 7.39 (2H, dt), 10.19 (1H, s).

(0383)

Step 2

Synthesis of 2-(2-(4-methoxybenzyl)-2H-tetrazolyl) phenylmethanol.

2-(4-methoxybenzyl)-2H-tetrazole-5-carbaldehyde 910 mg was dissolved in THF 20ml, and phenylmagnesium bromide (THF solution of 1M) 5 ml under stirring were added at 0°C. The reaction liquor was stirred at the same temperature for one hour, and thereafter, saturated ammonium chloride aqueous solution 30 ml were added. The mixed liquid was extracted with ethyl acetate, and extract layer was washed with saturated aqueous sodium chloride solution, and thereafter, drying with magnesium sulfate was carried out. The solvent was eliminated by distillation, and the obtained residue was purified by column chromatography (eluate = n-hexane : ethyl acetate = 4 : 1) using silica gel, and 2-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) phenylmethanol 916 mg was obtained as an oily substance.
NMR (400 MHz, CDCl3) δ ppm 3.01 (1H, br s), 3.79 (3H, s), 5.65 and 5.67 (2H, each d), 6.11 (1H, d), 6.88 (2H, dt), 7.25-7.48 (7H, m).

(0384)

Step 3

Synthesis of 5-benzoyl-2-(4-methoxybenzyl)-2H-tetrazole.

2-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) phenylmethanol was oxidised with active manganese dioxide in the same way as in Step 1, and 5-benzoyl-2-(4-methoxybenzyl)-2H-tetrazole was obtained.
mp. 61-62°C,
NMR (400 MHz, CDCl3) δ ppm 3.80 (3H, s), 5.82 (2H, s), 6.91 (2H, d), 7.42 (2H, dt), 7.53 (2H, t), 7.67 (1H, t), 8.34 (2H, d).

(0385)

Step 4

Synthesis of (Z)-ethyl 3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) cinnamic acid.

Sodium hydride (60 % oiliness) 148 mg was suspended in THF 15ml, and triethyl phosphono acetic acid 832 mg was added at 0°C, and the mixture was stirred for one hour. To the reaction liquor, 5-benzoyl-2-(4-methoxybenzyl)-2H-tetrazole 909mgTHF 5ml solution was added at 0°C and also was stirred at the same temperature for one hour. Water 30 ml were added to the reaction liquor and extraction was carried out with ethyl acetate. The liquid extract was washed with saturated aqueous sodium chloride solution, and thereafter, drying with magnesium sulfate was carried out. The residue obtained by elimination of the solvent by distillation was purified by column chromatography (eluate = n-hexane : ethyl acetate = 4 : 1) using silica gel, and (Z)-ethyl 3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) cinnamic acid 900 mg was obtained as an oily substance.
NMR (400 MHz, CDCl3) δ ppm 1.05 (3H, t), 3.76 (3H, s), 4.01 (2H, q), 5.77 (2H, s), 6.62 (1H, s), 6.89 (2H, d), 7.29-7.49 (7H, m).

(0386)

Step 5

Synthesis of (Z)-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) cinnamic acid.

(Z)-ethyl 3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) cinnamic acid was treated in the same way as in Example 56, and (Z)-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) cinnamic acid was obtained.

mp. 126°C,

IR v max cm-1 2596, 1712,

NMR (400 MHz, CDCl3) δ ppm 3.79 (3H, s), 5.76 (2H, s), 6.62 (1H, s), 6.89 (2H, d), 7.27-7.54 (7H, m),

MS(FAB)m/z 336 (M+ +1),

Elemental analysis values as C18H16N4 O3

Theoretical values (%) C, 64.28, H, 4.79,N, 16.66,

Measured values (%) C, 64.02, H, 4.93, N, 16.61..

(0387)

Synthesis of (Z)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) cinnamide

3-(2-(2-benzothiazole) ethinyl) aniline and (Z)-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) cinnamic acid were treated in the same way as in Step 1 of Example 103, and (Z)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) cinnamide was obtained as a straw-coloured oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.89-2.41 (6H, m), 3.70 (1H, m), 3.76 (3H, s), 5.74 (2H, s), 6.74 (1H, s), 6.82 (2H, d), 6.96 (1H, s), 7.27-7.40 (9H, m), 7.55 (1H, d), 7.76 (1H, s), 7.96 (1H, s).

(0388)

Step 7

Synthesis of (Z)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(1H-tetrazol-5-yl) cinnamide.

(Z)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) cinnamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 127-129°C (chloroform - n-hexane = recrystallization solvent),

NMR (400 MHz, DMSO-d6) δ ppm 1.85-2.33 (6H, m), 3.66 (1H, m), 7.14 (1H, s), 7.30-7.59 (8H, m), 7.93 (1H, s), 10.69 (1H, s),

MS(FAB)m/z 453 (M+ +1).

(0389)

Example 125

(E)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-3-(1H-tetrazol-5-yl) propenamide:

Step 1

Synthesis of (E)-ethyl 2-fluoro-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) acrylic acid.

2-(4-methoxybenzyl)-2H-tetrazole-5-carbaldehyde and triethyl 2-fluorophenoacetic acid were treated in the same way as in Step 4 of Example 124, and (E)-ethyl 2-fluoro-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) propenamide was obtained as an oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.16 (3H, t), 3.80 (3H, s), 4.22 (2H, q), 5.70 (2H, s), 6.73 (1H, d), 6.89 (2H, d), 7.34 (2H, d).

(0390)

Step 2

Synthesis of (E)-2-fluoro-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) acrylic acid.

Ethyl (E)-2-fluoro-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) acrylic acid was treated in the same way as in Example 56, and (E)-2-fluoro-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) acrylic acid was obtained.

mp. 65°C,

IR v max cm-1 2952, 2844, 2728, 2616, 2532, 1750,

NMR (400 MHz, CDCl3) δ ppm 3.82 (3H, s), 5.77 (2H, s), 6.93 (2H, d), 7.00 (1H, d), 7.38 (2H, d),

Elemental analysis values as C12H11FN4 O3

Theoretical values (%) C, 51.80, H, 3.98, N, 20.14,

Measured values (%) C, 51.92, H, 4.09, N, 20.22..

(0391)

Step 3

Synthesis of (E)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) propenamide.

3-(2-(2-benzothiazole) ethinyl) aniline and (E)-2-fluoro-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) acrylic acid were treated in the same way as in Step 1 of Example 103, and (E)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) propenamide was obtained as a pale yellow oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.90-2.42 (6H, m), 3.70 (1H, m), 3.80 (3H, s), 5.78 (2H, s), 6.90-7.00 (4H, m), 7.35-7.41 (4H, m), 7.84 (1H, dt), 7.95 (1H, s), 11.74 (1H, s).

(0392)

Step 4

Synthesis of (E)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-3-(1H-tetrazol-5-yl) propenamide.

(E)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) propenamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 211-212°C (recrystallization solvent = chloroform - n-hexane),

IR v max cm-1 2212, 1672,

NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.33 (6H, m), 3.67 (1H, m), 7.23 (1H, d), 7.45-7.54 (3H, m), 7.74 (1H, d), 8.07 (1H, s), 11.14 (1H, s),

MS(FAB)m/z 395 (M+ +1),

Elemental analysis values as C19H15FN6 OS • 1/2 H2O

Theoretical values (%) C, 56.57, H, 4.00, N, 20.83,

Measured values (%) C, 56.37, H, 3.87, N, 20.67..

(0393)

Example 126

(Z)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-3-(1H-tetrazol-5-yl) propenamide:

Step 1

Synthesis of (Z)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) propenamide.

Z-isomer was separated with Step 3 of Example 125, and (Z)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) propenamide was obtained as a pale yellow oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.92-2.44 (6H, m), 3.70 (1H, m), 3.81 (3H, s), 5.75 (2H, s), 6.91 (2H, d), 6.97 (1H, s), 7.35-7.43 (4H, m), 7.68 (1H, m), 7.87 (1H, d), 8.10 (1H, m).

(0394)

Step 2

Synthesis of (Z)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-3-(1H-tetrazol-5-yl) propenamide.

(Z)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) propenamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 125-128°C,

Elemental analysis values as C19H15FN6 OS • 1/2 H2O

Theoretical values (%) C, 56.57, H, 4.00, N, 20.83,

Measured values (%) C, 56.86, H, 4.29, N, 20.00..

(0395)

Example 127

(E)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-3-(1H-tetrazol-5-yl)-2-butene amide:

Step 1

Synthesis of 1-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) ethanol.

2-(4-methoxybenzyl)-2H-tetrazole-5-carbaldehyde and methyl magnesium bromide (ether solution of 3M) were treated in the same way as in Step 2 of Example 124, and 1-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) ethanol was obtained.

mp. 61-62°C,

NMR (400 MHz, CDCl3) δ ppm 1.65 (3H, d), 2.56 (1H, d), 3.80 (3H, s), 5.16 (1H, m), 5.67 (2H, s), 6.89 (2H, dt), 7.34 (2H, dt).

(0396)

Step 2

Synthesis of 2-acetyl-2-(4-methoxybenzyl)-2H-tetrazole.

1-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) ethanol was treated in the same way as in Step 3 of Example 124, and 2-acetyl-2-(4-methoxybenzyl)-2H-tetrazole was obtained.

mp. 66-67°C,

IR v max cm-1 1718,

NMR (400 MHz, CDCl3) δ ppm 2.74 (3H, s), 3.80 (3H, s), 5.77 (2H, s), 6.90 (2H, d), 7.39 (2H, d).

(0397)

Step 3

Synthesis of ethyl (E)-2-fluoro-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-butenoic acid.

2-acetyl-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 1 of Example 125, and ethyl (E)-2-fluoro-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-butenoic acid was obtained as an oily substance.
NMR (400 MHz, CDCl3) δ ppm 1.00 (3H, t), 2.17 (3H, d), 3.80 (3H, s), 4.04 (2H, q), 5.70 (2H, s), 6.90 (2H, d), 7.36 (2H, d).

(0398)

Step 4

Synthesis of (E)-2-fluoro-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-butenoic acid.

Ethyl (E)-2-fluoro-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-butenoic acid was processed in the same way as in Example 56, and (E)-2-fluoro-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-butenoic acid was obtained as an oily substance.
NMR (400 MHz, CDCl3) δ ppm 2.36 (3H, d), 3.81 (3H, s), 5.76 (2H, s), 6.93 (2H, d), 7.38 (2H, d).

(0399)

Step 5

Synthesis of (E)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-butene amide.

3-(2-(2-benzothiazole) ethinyl) aniline and (E)-2-fluoro-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) butenoic acid were processed in the same way as in Step 1 of Example 103, and (E)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) butene amide was obtained as a pale yellow oily substance.
NMR (400 MHz, CDCl3) δ ppm 1.89-2.39 (6H, m), 3.69 (1H, m), 3.78 (3H, s), 5.74 (2H, s), 6.89 (2H, dt), 7.29-7.40 (4H, m), 7.59 (1H, d), 7.81 (1H, s), 9.24 (1H, s).

(0400)

Step 6

Synthesis of (E)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-3-(1H-tetrazol-5-yl) butene amide.

(E)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) butene amide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 199-200°C,
IR v max cm-1 2216, 1672,
NMR (400 MHz, DMSO-d6) δ ppm 1.88-2.27 (6H, m), 3.66 (1H, m), 7.42-7.47 (2H, m), 7.52 (1H, s), 7.68 (1H, d), 7.93 (1H, s), 10.74 (1H, s),

MS(FAB)m/z 409 (M+ +1),
Elemental analysis values as C20H17FN6 OS • 3/4 H2O
Theoretical values (%) C, 56.93, H, 4.42, N, 19.92,
Measured values (%) C, 57.13,H, 4.18, N, 19.80..

(0401)

Example 128

(E)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(1H-tetrazol-5-yl)-2-propenamide;

Step 1

Synthesis of ethyl (E)-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) acrylic acid.

2-(4-methoxybenzyl)-2H-tetrazole-5-carbaldehyde and triethykphenoacetic acid were treated in the same way as in Step 4 of Example 124, and ethyl (E)-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) acrylic acid was obtained.
mp. 36°C,
NMR (400 MHz, CDCl3) δ ppm 1.33 (3H, t), 3.80 (3H, s), 4.27 (2H, q), 5.70 (2H, s), 6.90 (2H, dt), 7.35 (2H, dt), 7.66 (1H, d).

(0402)

Step 2

Synthesis of (E)-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) acrylic acid.

Ethyl (E)-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) acrylic acid was treated in the same way as in Example 56, and (E)-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) acrylic acid was obtained.
mp. 167-169°C,
IR v max cm-1 2688, 2268, 2556, 1694,
NMR (400 MHz, CDCl3) δ ppm 3.80 (3H, s), 5.71 (2H, s), 6.90 (2H, d), 7.36 (2H, dt), 7.76 (1H, d),
MS(FAB)m/z 261 (M+ +1),
Elemental analysis values as C12H12N4 O3
Theoretical values (%) C, 55.38, H, 4.65, N, 21.53,
Measured values (%) C, 55.34,H, 4.70, N, 21.63..

(0403)

Step 3

Synthesis of (E)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-propenamide.

(E)-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) acrylic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) aniline were treated in the same way as in Step 1 of Example 103, and (E)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-propenamide was obtained as a straw-coloured oily substance.
NMR (400 MHz, CDCl3) δ ppm 1.94-2.36 (6H, m), 3.70 (1H, m), 3.81 (3H, s), 5.71 (2H, s), 6.96 (1H, s), 7.14 (2H, d), 7.34 (4H, m), 7.40 (1H, m), 7.77 (1H, d), 7.83 (1H, s).

(0404)

Step 4

Synthesis of (E)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(1H-tetrazol-5-yl)-2-propenamide.

(E)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-propenamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. >300°C,
IR v max cm-1 2212, 1674,
NMR (400 MHz, CDCl3) δ ppm 1.84-2.31 (6H, m), 3.67 (1H, m), 7.30-7.59 (5H, m), 7.71 (1H, d), 8.09 (1H, s), 10.75 (1H, s),
MS(FAB)m/z 377 (M+ +1),
Elemental analysis values as C19H16N6 OS • 1/2 H2O
Theoretical values (%) C, 59.21, H, 4.45, N, 21.80,
Measured values (%) C, 59.03, H, 4.29, N, 21.66..

(0405)

Example 129

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(1H-tetrazol-5-yl)-1-cyclopentene-1-carboxamide:

Step 1

Synthesis of ethyl 2-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-1-cyclopentene-1-carboxylate.
Ethyl 2-cyano-1-cyclopentene-1-carboxylate was processed in the same way as in Reference Example 20, and ethyl 2-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-1-cyclopentene-1-carboxylate was obtained as an oily substance.
NMR (400 MHz, CDCl3) δ ppm 1.13 (3H, t), 2.05 (2H, q), 2.85 (2H, t), 2.96 (2H, t), 3.79 (3H, s), 4.15 (2H, q), 5.68 (2H, s), 6.86 (2H, d), 7, 32 (2H, d).

(0406)

Step 2

Synthesis of 2-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-1-cyclopentene-1-carboxylic acid.

Ethyl 2-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-1-cyclopentene-1-carboxylate was processed in the same way as in Example 56, and 2-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-1-cyclopentene-1-carboxylic acid was obtained.

mp. 106-108°C,

NMR (400 MHz, CDCl3) δ ppm 1.99 (2H, q), 2.93-3.03 (2H, m), 3.10-3.33 (2H, m), 3.80 (3H, s), 5.71 (2H, s), 6.91 (2H, d), 7, 37 (2H, d),

Elemental analysis values as C15H16N4 O3

Theoretical values (%) C, 59.99, H, 5.37, N, 18.66,

Measured values (%) C, 59.69, H, 5.37, N, 18.19..

(0407)

Step 3

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-1-cyclopentene-1-carboxamide.

2-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-1-cyclopentene-1-carboxylic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 1 of Example 103, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-1-cyclopentene-1-carboxamide was obtained as a pale yellow oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.8-2.11 (2H, m), 2.28-2.41 (4H, m), 3.08 (2H, t), 3.16 (2H, t), 3.68 (1H, m), 3.79 (3H, s), 5.76 (2H, s), 6.90 (2H, d), 6.95 (1H, s), 7, 29-7.33 (2H, m), 7.37 (2H, d), 7.78-7.81 (1H, m), 7.96 (1H, s), 11.58 (1H, s).

(0408)

Step 4

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(1H-tetrazol-5-yl)-1-cyclopentene-1-carboxamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-1-cyclopentene-1-carboxamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 186-189°C (decomp),

NMR (400 MHz, DMSO-d6) δ ppm 1.81-2.09 (2H, m), 2.21-2.28 (4H, m), 2.94-2.99 (4H, m), 3.67 (1H, m), 7.38 (1H, d), 7.44 (1H, t), 7.53 (1H, s), 7.67 (1H, d), 8.02 (1H, s), 10.46 (1H, s), 7.30-7.59 (5H, m), 7.71 (1H, d), 8.09 (1H, s), 10.75 (1H, s),

Elemental analysis values as C22H20N6OS • 1/4 H2O

Theoretical values (%) C, 62.76, H, 4.91, N, 19.96,

Measured values (%) C, 62.56, H, 5.04, N, 19.53..

(0409)

Example 130

(E, E)-N-(3-(2-(4-isopropyl-2-thiazolyl) ethinyl) phenyl)-5-(1H-tetrazol-5-yl)-2,4-penta dien amide:

Step 1

Synthesis of (E, E)-N-(3-(2-(4-isopropyl-2-thiazolyl) ethinyl) phenyl)-5-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2,4-penta dien amide.

3-(2-(4-isopropyl-2-thiazolyl) ethinyl) aniline and (E, E)-5-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2,4-penta dien amide which it was treated in the same way as in Reference Example 17, and was obtained were treated in the same way as in Step 1 of Example 103, and (E, E)-N-(3-(2-(4-isopropyl-2-thiazolyl) ethinyl) phenyl)-5-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2,4-penta dien amide was obtained.

mp. 150-151°C,

IR v max cm-1 2212, 1678,

NMR (400 MHz, CDCl3) δ ppm 1.35 (6H, d), 3.15 (1H, m), 3.80 (3H, s), 5.69 (2H, s), 6.90 (2H, d), 6.94 (1H, s), 6.95 (1H, d), 7.18-7.68 (8H, m), 7.79 (1H, br s),

MS(FAB)m/z 511 (M+ +1),

Elemental analysis values as C28H26N6 O2S

Theoretical values (%) C, 65.86, H, 5.13, N, 16.46,

Measured values (%) C, 65.60, H, 5.10, N, 16.72..

(0410)

Step 2

Synthesis of (E, E)-N-(3-(2-(4-isopropyl-2-thiazolyl) ethinyl) phenyl)-5-(1H-tetrazol-5-yl)-2,4-penta dien amide.

(E, E)-N-(3-(2-(4-isopropyl-2-thiazolyl) ethinyl) phenyl)-5-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2,4-penta dien amide was processed in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 212-214°C (recrystallization solvent = chloroform-methanol),

NMR (400 MHz, DMSO-d6) δ ppm 1.27 (6H, d), 3.08 (1H, m), 6.54 (1H, d), 7.22 (1H, d), 7.36-7.54 (5H, m), 7.69 (1H, d), 8.07 (1H, s), 10.46 (1H, s),

Elemental analysis values as C20H18N6 OS

Theoretical values (%) C, 61.52, H, 4.65, N, 21.52,

Measured values (%) C, 61.50, H, 4.73, N, 21.52..

(0411)

Example 131

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzoyl-1H-tetrazole:

Step 1

Synthesis of 5-(3-iodobenzo yl)-1-(4-methoxybenzyl)-1H-tetrazole.

THF10ml and N, N'-tetramethylethylenediamine 1 ml was added to 3-iodo-N-methoxy-N-methylbenzamide 582 mg and 1-(4-methoxybenzyl)-1H-tetrazole 380 mg, and five minutes were needed, and lithium hexamethyl disilazide (THF solution of 1M) 2 ml were added dropwise by-78°C under stirring. Also the reaction liquor was stirred at the same temperature for 30 minutes, and thereafter, saturated ammonium chloride 10 ml were added, and it was returned to room temperature. The reaction liquor was extracted with ethyl acetate, and the extract was washed with saturated aqueous sodium chloride solution and thereafter, was dried with sodium sulfate. The residue obtained by elimination by distillation of the solvent was purified by column chromatography (eluate = n-hexane : ethyl acetate = 5 : 1) using silica gel, and 5-(3-iodobenzo yl)-1-(4-methoxybenzyl)-1H-tetrazole was obtained.

mp. 86-89°C,

NMR (400 MHz, CDCl3) δ ppm 3.76 (3H, s), 5.88 (2H, s), 6.83-6.85 (2H, m), 7.27 (1H, t), 7.34-7.37 (2H, m), 8.00 (1H, d), 8.41 (1H, d), 8.67 (1H, s).

(0412)

Step 2

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzoyl)-1-(4-methoxybenzyl)-1H-tetrazole.

5-(3-iodobenzo yl)-1-(4-methoxybenzyl)-1H-tetrazole and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 4 of Example 1, and 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzoyl)-1-(4-methoxybenzyl)-1H-tetrazole was obtained.

mp. 83-86°C,

NMR (400 MHz, CDCl3) δ ppm 1.92-2.40 (6H, m), 3.66-3.76 (1H, m), 3.76 (3H, s), 5.90 (2H, s), 6.83-6.86 (2H, m), 6.99 (1H, s), 7.35-7.37 (2H, m), 7.55 (1H, t), 7.87 (1H, d), 8.42 (1H, d), 8.59 (1H, s).

(0413)

Step 3

Synthesis of 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzoyl-1H-tetrazole.

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzoyl)-1-(4-methoxybenzyl)-1H-tetrazole was

treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 191-196°C (decomp) (recrystallization solvent = chloroform-n-hexane),
IR v max cm-1 3112, 3088, 2944, 2220, 1668, 1596, 1504,
NMR (400 MHz, DMSO-d6) δ ppm 1.85-2.32 (6H, m), 3.64-3.72 (1H, m), 7.56 (1H, s), 7.75 (1H, t), 8.04 (1H, d), 8.44 (1H, d), 8.64 (1H, s),
MS(EI)m/z 335(M+),
Elemental analysis values as C17H13N5 OS
Theoretical values (%) C, 60.88, H, 3.91, N, 20.88,
Measured values (%) C, 60.61, H, 3.95, N, 20.82..

(0414)

Example 132

Ethyl (E)-3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(1H-tetrazol-5-yl) propenoic acid:

Step 1

Synthesis of ethyl (E)-3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl) propenoic acid.

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzoyl)-1-(4-methoxybenzyl)-1H-tetrazole and triethyl phosphono acetic acid were treated in the same way as in Step 4 of Example 124, and ethyl (E)-3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl) propenoic acid was obtained as an oily substance.
NMR (400 MHz, CDCl3) δ ppm 1.15 (3H, t), 1.84-2.39 (6H, m), 3.65-3.73 (1H, m), 3.75 (3H, s), 4.12 (2H, q), 5.07 (2H, s), 6.67 (1H, s), 6.77-6.82 (2H, m), 6.99 (1H, s), 7.19 (1H, d), 7.32 (1H, s), 7.38 (1H, t), 7.64 (1H, d).

(0415)

Step 2

Synthesis of ethyl (E)-3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(1H-tetrazol-5-yl) propenoate.

Ethyl (E)-3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl) propenoate was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 122-124°C (recrystallization solvent = chloroform-n-hexane),
IR v max cm-1 2216, 1724,
NMR (400 MHz, CDCl3) δ ppm 1.10 (3H, t), 1.86-2.37 (6H, m), 3.58-3.67 (1H, m), 4.07 (2H, q), 6.98 (1H, s), 7.23 (1H, s), 7.30-7.44 (4H, m),
MS(EI)m/z 405(M+),

Elemental analysis values as C21H19N5 O2 S
Theoretical values (%) C, 62.21, H, 4.72, N, 17.27,
Measured values (%) C, 62.06, H, 4.66, N, 17.02..

(0416)

Example 133

3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(1H-tetrazol-5-yl) propenoic acid :

Ethyl (E)-3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(1H-tetrazol-5-yl) propenoic acid was treated in the same way as in Example 56, and the title substance was obtained.
mp. >300°C (recrystallization solvent = chloroform-ethanol),
IR v max cm-1 2218, 1707, 1629,
NMR (400 MHz, DMSO-d6) δ ppm 1.88-2.33 (6H, m), 3.64-3.68 (1H, m), 6.99 (1H, s), 7.43 (1H, d), 7.52 (1H, t), 7.52 (1H, s), 7.61 (1H, s), 7.70 (1H, d),
MS(FAB)m/z 378 (M+ +1),
Elemental analysis values as C19H15N5 O2 S
Theoretical values (%) C, 60.46, H, 4.01, N, 18.56,
Measured values (%) C, 60.52, H, 4.15, N, 18.65..

(0417)

Example 134

(E)-3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(1H-tetrazol-5-yl) acrylonitrile:

Step 1

Synthesis of (E)-3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl) acrylonitrile.

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzoyl)-1-(4-methoxybenzyl)-1H-tetrazole and diethyl cyanomethylphosphonate were treated in the same way as in Step 4 of Example 124, and (E)-3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl) acrylonitrile was obtained as an oily substance.
NMR (400 MHz, CDCl3) δ ppm 1.92-2.40 (6H, m), 3.70-3.76 (1H, m), 3.76 (3H, s), 5.08 (2H, s), 6.14 (1H, s), 6.62-6.79 (4H, m), 7.00 (1H, s), 7.40-7.42 (2H, m), 7.51 (1H, t), 7.75 (1H, d).

(0418)

Step 2

Synthesis of (E)-3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(1H-tetrazol-5-yl) acrylonitrile.

(E)-3-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl)

acrylonitrile was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 179-182°C (decomp) (recrystallization solvent = chloroform-ethanol-n-hexane),

IR v max cm-1 2220,

NMR (400 MHz, DMSO-d6) δ ppm 1.83-2.32 (6H, m), 3.62-3.71 (1H, m), 6.93 (1H, s), 7.54 (1H, s), 7.43 (1H, d), 7.52 (1H, t), 7.52 (1H, s), 7.66 (1H, t), 7.71 (1H, d), 7.85 (1H, d), 7.88 (1H, s),

MS(FAB)m/z 359 (M+ +1),

Elemental analysis values as C19H14N6 S

Theoretical values (%) C, 62.88, H, 4.03, N, 23.16,

Measured values (%) C, 62.88, H, 4.02, N, 23.13..

(0419)

Example 135

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) amino-1H-tetrazole:

Step 1

Synthesis of 5-(3-iodo phenyl) amino-1-(4-methoxybenzyl)-1H-tetrazole and 5-(3-iodo phenyl) amino-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-iodo phenyl) amino-1H-tetrazole was treated in the same way as in Step 3 of Example 1, and 5-(3-iodo phenyl) amino-1-(4-methoxybenzyl)-1H-tetrazole and 5-(3-iodo phenyl) amino-2-(4-methoxybenzyl)-2H-tetrazole were obtained.

mp. 138-139°C,

NMR (400 MHz, CDCl3) δ ppm 3.81 (3H, s), 5.61 (2H, s), 6.86 (1H, s), 6.92 (2H, d), 7.03 (1H, t), 7.31 (1H, dd), 7.37 (1H, dd), 7.38 (2H, d), 7.83 (1H, t).

(0420)

Step 2

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) amino-1-(4-methoxybenzyl)-1H-tetrazole and 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) amino-2-(4-methoxybenzyl)-2H-tetrazole.

The aforesaid iodine compound and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) amino-1-(4-methoxybenzyl)-1H-tetrazole and 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) amino-2-(4-methoxybenzyl)-2H-tetrazole were obtained as an oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.90-2.50 (6H, m), 3.60-3.70 (1H, m), 3.80 (3H, s), 5.64 (2H, s), 6.91 (2H, d), 6.96 (1H, s), 7.16 (1H, s), 7.21 (1H, dd), 7.32 (1H, t), 7.39 (2H, d), 7.43 (1H, dd), 7.71 (1H, t).

(0421)

Step 3

Synthesis of 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) amino-1H-tetrazole.

Compound obtained in the aforesaid Step 2 was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 133-135°C (recrystallization solvent : chloroform-ethanol),

NMR (400 MHz, DMSO-d6) δ ppm 1.80-2.40 (6H, m), 3.20-3.40 (1H, br s), 3.60-3.80 (1H, m), 7.22 (1H, d), 7.42 (1H, t), 7.53 (1H, s), 7.86 (1H, s), 10.09 (1H, s),

MS(FAB)m/z 323 (M+ +1).

(0422)

Example 136

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenoxy)-1H-tetrazole:

Step 1

Synthesis of 5-(3-iodo phenoxy)-1-(4-methoxybenzyl)-1H-tetrazole.

DMF 20 ml were added to 5-iodo-1-(4-methoxybenzyl)-1H-tetrazole 948 g, 3-iodo phenol 741 mg and potassium carbonate 1.24 g and were stirred at 70°C for three days. The reaction liquor was discharged into water 200 ml and extraction was carried out with ethyl acetate. The extract layer was washed with water and thereafter, was dried with sodium sulfate. Residue obtained by elimination by distillation of the solvent was purified by column chromatography (eluate = chloroform) using silica gel, and 5-(3-iodo phenoxy)-1-(4-methoxybenzyl)-1H-tetrazole was obtained as an oily substance.

NMR (400 MHz, CDCl3) δ ppm 3.80 (3H, s), 5.37 (2H, s), 6.91-6.87 (2H, m), 7.13 (1H, t), 7.30-7.34 (3H, m), 7.60 (1H, d), 7.64 (1H, s).

(0423)

Step 2

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenoxy)-1-(4-methoxybenzyl) 1-H-tetrazole.

5-(3-iodo phenoxy)-1-(4-methoxybenzyl)-1H-tetrazole and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenoxy)-1-(4-methoxybenzyl) 1-H-tetrazole was obtained as reddish brown oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.89-2.40 (6H, m), 3.65-3.74 (1H, m), 3.81 (3H, s), 5.39 (2H, s), 6.90-6.92 (2H, m), 6.98 (1H, m), 7.32-7.34 (2H, m), 7.40-7, 44 (2H, m), 7.48-7.50 (1H, m), 7.53 (1H, s).

(0424)

Step 3

Synthesis of 5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenoxy)-1H-tetrazole.

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenoxy)-1-(4-methoxybenzyl) 1-H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 161-163°C (recrystallization solvent = chloroform-n-hexane),

IR v max cm-1 2212,

NMR (400 MHz, DMSO-d6) δ ppm 1.83-2.30 (6H, m), 3.63-3.71 (1H, m), 7.48-7.58 (4H, m), 7.68 (1H, s),

MS(EI)m/z 323(M+),

Elemental analysis values as C16H13N5 OS/1 /4 H2 O

Theoretical values (%) C, 58.61, H, 4.15, N, 21.36,

Measured values (%) C, 58.85, H, 4.10, N, 21.32..

(0425)

Example 137

5-(3-(2-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) ethinyl) phenyl)-1H-tetrazole:

Step 1

Synthesis of 5-(3-(2-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole.

5-(3-ethinyl phenyl)-2-(4-methoxybenzyl)-2H-tetrazole and 1-bromo-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzene were treated in the same way as in Step 4 of Example 1, and 5-(3-(2-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was obtained as a yellow oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.90-2.50 (6H, m), 3.60-3.80 (1H, m), 3.81 (3H, s), 5.75 (2H, s), 6.92 (2H, d), 6.98 (1H, m), 7.30-7.40 (3H, m), 7.49 (1H, t), 7.50-7.60 (2H, m), 7.60 (1H, d), 7.77 (1H, s), 8.12 (1H, d), 8.32 (1H, s).

(0426)

Step 2

Synthesis of 5-(3-(2-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) ethinyl) phenyl)-1H-tetrazole.

5-(3-(2-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) ethinyl) phenyl)-2-(4-methoxybenzyl)-2H-tetrazole was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 106-108°C (decomp) (recrystallization solvent = chloroform-n-hexane),
NMR (400 MHz, DMSO-d6) δ ppm 1.80-2.40 (6H, m), 3.60-3.80 (1H, m), 7.70 (1H, s), 7.74 (1H, t), 7.60-7.80 (3H, m), 7.80 (1H, d), 7.90 (1H, s), 8.11 (1H, d), 8.25 (1H, s),
MS(FAB)m/z 408 (M+ +1),
Elemental analysis values as C24H17N5 S
Theoretical values (%) C, 58.25, H, 3.77, N, 12.82,
Measured values (%) C, 58.51, H, 3.52, N, 12.82..

(0427)

Example 138

N-(1H-tetrazol-5-yl)-4-((3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) amino sulphonyl) benzamide:

Step 1

Synthesis of 4-((3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) amino sulphonyl) benzoic acid.

(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline 293 ml and pyridine are dissolved in methylene chloride 10 ml, and 4-chloro sulphonyl benzoic acid 254 mg is added and reaction mixture is stirred at room temperature for 1 hour. To the reaction solution is added 1N hydrochloric acid 10 ml and it is extracted with methylene chloride. The liquid extract was washed with saturated aqueous sodium chloride solution and thereafter, was dried with sodium sulfate. the solvent was eliminated by distillation, and obtained crude crystals were recrystallised from chloroform-n-hexane, and 4-((3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) amino sulphonyl) benzoic acid was obtained.
mp. 213-216°C (decomp),
IR v max cm-1 2216, 1704, 1602, 1580, 1504, 1338,
NMR (400 MHz, DMSO-d6) δ ppm 1.89-2.33 (6H, m), 3.64 (1H, m), 7.21-7.24 (1H, m), 7.31-7.40 (3H, m), 7.54 (1H, s), 7.90 (1H, d), 8.10 (1H, d), 10.76 (1H, s), MS(FAB). m/z 439 (M+ +1),
Elemental analysis values as C22H18N2 O4 S2/H2 O
Theoretical values (%) C, 57.88, H, 4.42, N, 6.14,
Measured values (%) C, 58.02, H, 4.13, N, 5.86..

(0428)

Step 2

Synthesis of N-(1H-tetrazol-5-yl)-4-((3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) amino sulphonyl) benzamide.

4-((3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) amino sulphonyl) benzoic acid and 5-amino-

1H-tetrazole were treated in the same way as in Example 86, and the title substance was obtained.
mp. 203-206°C (decomp) (chloroform-ethanol-n-hexane = recrystallization solvent),
IR v max cm-1 2216, 1692, 1588, 1548, 1504, 1406, 1338,
NMR (400 MHz, DMSO-d6) δ ppm 1.83-2.33 (6H, m), 3.66 (1H, m), 7.26 (1H, dt), 7.30-7.39 (3H, m), 7.53 (1H, s), 7.96 (1H, d), 8.20 (1H, d), 10.78 (1H, s), 12.63 (1H, br),
MS(FAB)m/z 506 (M+ +1),
Elemental analysis values as C23H29N7 O3 S2
Theoretical values (%) C, 54.64, H, 3.78, N, 19.39,
Measured values (%) C, 54.24, H, 3.83, N, 18.98..

(0429)

Example 139

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-(1H-tetrazol-5-yl) benzene sulphonamide:

Step 1

Synthesis of N-(3-iodo phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzene sulphonamide.

N-(3-iodo phenyl)-4-(1H-tetrazol-5-yl) benzene sulphonamide was treated in the same way as in Step 3 of Example 1, and N-(3-iodo phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzene sulphonamide was obtained.
mp. 139-140°C (recrystallization solvent = methylene chloride),
NMR (400 MHz, CDCl3) δ ppm 3.80 (3H, s), 5.74 (2H, s), 6.73 (1H, s), 6.90 (2H, d), 6.95 (1H, t), 7.05-7.07 (1H, m), 7.38 (2H, d), 7.44-7.46 (2H, m), 7.86 (2H, d), 8.23 (2H, d),
MS(FAB)m/z 538 (M+ +1),
Elemental analysis values as C21H18IN5 O3 S
Theoretical values (%) C, 46.08, H, 3.31, N, 12.79,
Measured values (%) C, 46.87, H, 3.67, N, 12.15..

(0430)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzene sulphonamide.

N-(3-iodo phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzene sulphonamide and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzene sulphonamide was obtained.
mp. 130-132°C (recrystallization solvent = chloroform-n-hexane),

IR v max cm-1 2216,

NMR (400 MHz, CDCl3) δ ppm 1.88-2.40 (6H, m), 3.69 (1H, m), 3.79 (3H, s), 5.73 (2H, s), 6.80 (1H, br s), 6.89 (2H, d), 7.00 (1H, s), 7.14 (1H, d), 7.21 (1H, t), 7.29 (1H, t), 7.32 (1H, d), 7.38 (2H, d), 7.84 (2H, d), 8.19 (2H, d),

MS(FAB)m/z 583 (M+ +1),

Elemental analysis values as C30H26N6 O3 S2/H2 O

Theoretical values (%) C, 59.99, H, 4.70,N, 13.99,

Measured values (%) C, 59.91, H, 4.37, N, 13.88..

(0431)

Step 3

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-4-(1H-tetrazol-5-yl) benzene sulphonamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzene sulphonamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 172-175°C (decomp) (recrystallization solvent: chloroform-n-hexane),

IR v max cm-1 2216, 1656, 1602, 1576, 1538, 1352,

NMR (400 MHz, CDCl3) δ ppm 1.88-2.40 (6H, m), 3.69 (1H, m), 3.79 (3H, s), 5.73 (2H, s), 6.80 (1H, br s), 6.89 (2H, d), 7.00 (1H, s), 7.14 (1H, d), 7.21 (1H, t), 7.29 (1H, t), 7.32 (1H, d), 7.38 (2H, d), 7.84 (2H, d), 8.19 (2H, d),

MS(FAB)m/z 463 (M+ +1),

Elemental analysis values as C22H18N6 O2 S2/1 /2 H2 O

Theoretical values (%) C, 56.04, H, 4.06,N, 17.82,

Measured values (%) C, 56.12, H, 3.93,N, 17.94..

(0432)

Example 140

N-(4-(1H-tetrazol-5-yl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzene sulphonamide:

Step 1

Synthesis of N-(4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-3-bromobenzene sulphonamide.

N-(4-(1H-tetrazol-5-yl)-3-bromobenzene sulphonamide was processed in the same way as in Step 3 of Example 1, and N-(4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-3-bromobenzene sulphonamide was obtained.

mp. 190-192°C (recrystallization solvent = methylene chloride-n-hexane),

IR v max cm-1 1614, 1516, 1348,

NMR (400 MHz, CDCl3) δ ppm 3.79 (3H, s), 5.71 (2H, s), 6.71 (1H, s), 6.89 (2H, d), 7.18 (2H, d), 7.30 (1H, t), 7.37 (2H, d), 7.67 (2H, d), 7.97 (1H, t), 8.03 (2H, d),
MS(FAB)m/z 501 (M+ +2) +1), 499((M+) +1).
Elemental analysis values as C21H18BrN5 O3 S
Theoretical values (%) C, 50.41, H, 3.63,N, 14.00,
Measured values (%) C, 50.73, H, 3.87, N, 13.99..

(0433)

Step 2

Synthesis of N-(4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-3-iodobenzene sulphonamide.

N-(4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-3-bromobenzene sulphonamide was treated in the same way as in Step 2 of Example 19, and N-(4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-3-iodobenzene sulphonamide was obtained.
mp. 197-201°C (recrystallization solvent = methylene chloride-n-hexane),
IR v max cm-1 1614, 1516, 1348,
NMR (400 MHz, CDCl3) δ ppm 3.79 (3H, s), 5.71 (2H, s), 6.89 (2H, d), 7.15 (1H, t), 7.17 (2H, d), 7.37 (2H, d), 7.69 (2H, d), 7.86 (1H, d), 8.03 (2H, d), 8.16 (2H, d),
MS(EI)m/z 547(M+),
Elemental analysis values as C21H18IN5 O3 S
Theoretical values (%) C, 46.08, H, 3.31,N, 12.79,
Measured values (%) C, 46.36, H, 3.48, N, 12.66..

(0434)

Step 3

Synthesis of N-(4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzene sulphonamide.

N-(4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-3-iodobenzene sulphonamide and 4-cyclobutyl-2-ethinyl thiazole were treated in the same way as in Step 4 of Example 1, and N-(4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzene sulphonamide was obtained.
mp. 167-169°C (recrystallization solvent = chloroform-n-hexane),
IR v max cm-1 2216, 1614, 1514, 1480, 1388, 1846,
NMR (400 MHz, CDCl3) δ ppm 1.89-2.40 (6H, m), 3.72 (1H, m), 3.79 (3H, s), 5.70 (2H, s), 6.88 (2H, d), 7.00 (1H, s), 7.07 (1H, s), 7.21 (2H, d), 7.36 (2H, d), 7.39 (1H, t), 7.57 (1H, dt), 7.72 (1H, dt), 8.03 (1H, t), 8.03 (2H, d),
MS(FAB)m/z 583 (M+ +1),
Elemental analysis values as C30H26N6 O3 S2/1 /4 H2 O

Theoretical values (%) C, 61.36, H, 4.55, N, 14.31,
Measured values (%) C, 61.21, H, 4.49, N, 14.31..

(0435)

Step 4

Synthesis of N-(4-(1H-tetrazol-5-yl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzene sulphonamide.

N-(4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzene sulphonamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 139-142°C (decomp) (recrystallization solvent: chloroform-n-hexane),
IR v max cm-1 2220,
NMR (400 MHz, DMSO-d6) δ ppm 1.83-2.34 (6H, m), 3.67 (1H, m), 7.34 (2H, d), 7.57 (1H, s), 7.68 (1H, t), 7.90-7.94 (4H, m), 8.06 (1H, t), 10.87 (1H, s),
MS(FAB)m/z 463 (M+ +1),
Elemental analysis values as C22H18N6 O2 S2/H2 O
Theoretical values (%) C, 54.99, H, 4.19,N, 17.14,
Measured values (%) C, 54.69, H, 3.97, N, 17.18..

(0436)

Example 141

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of 4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzoic acid.

Ethyl 4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzoate was treated in the same way as in Example 56, and 4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzoic acid was obtained.

NMR (400 MHz, DMSO-d6) δ ppm 3.75 (3H, s), 5.94 (2H, s), 6.96 (2H, d), 7.41 (2H, d), 8.11 (2H, d), 8.16 (2H, d),
Elemental analysis values as C16H14N4 O3
Theoretical values (%) C, 61.93, H, 4.55,N, 18.06,
Measured values (%) C, 61.59, H, 4.56, N, 17.80..

(0437)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was obtained as yellow foamed substance.

NMR (400 MHz, CDCl3) δ ppm 1.89-2.41 (6H, m), 3.70 (1H, m), 3.80 (3H, s), 5.76 (2H, s), 6.91 (2H, d), 6.96 (1H, s), 7.38-7.41 (4H, m), 7.71-7.75 (1H, br), 7.89 (1H, d), 7.97 (2H, d), 8.27 (2H, d),

MS(FAB)m/z 547 (M+ +1).

(0438)

Step 3

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(1H-tetrazol-5-yl) benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 225-227°C (recrystallization solvent = chloroform-methanol),

NMR (400 MHz, DMSO-d6) δ ppm 1.83-2.35 (6H, m), 3.68 (1H, m), 7.42 (1H, d), 7.50 (1H, t), 7.53 (1H, s), 7.89 (1H, dd), 8.16 (1H, d), 8.19 (2H, d), 8.23 (2H, d), 10.58 (1H, br),

MS(FAB)m/z 427 (M+ +1),

Elemental analysis values as C23H18N6 OS

Theoretical values (%) C, 64.77, H, 4.25,N, 19.70,

Measured values (%) C, 64.64, H, 4.33, N, 19.47..

(0439)

Example 142

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of 3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzoic acid.

Ethyl 3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzoate was treated in the same way as in Example 56, and 3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzoic acid was obtained.

NMR (400 MHz, DMSO-d6) δ ppm 3.75 (3H, s), 5.92 (2H, s), 6.97 (2H, d), 7.41 (2H, d), 7.69 (1H, t), 8.08 (1H, d), 8.27 (1H, d), 8.58 (1H, s).

(0440)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was obtained.

mp. 140-142°C,

NMR (400 MHz, CDCl3) δ ppm 1.92-2.39 (6H, m), 3.69 (1H, m), 3.80 (3H, s), 5.75 (2H, s), 6.91 (2H, d), 6.95 (1H, s), 7.35-7.41 (4H, m), 7.61 (1H, t), 7.73 (1H, m), 7.92 (1H, s), 8.02 (1H, d), 8.07 (1H, s), 8.31 (1H, d), 8.57 (1H, s).

(0441)

Step 3

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 168-170°C,

NMR (400 MHz, DMSO-d6) δ ppm 1.87-2.31 (6H, m), 3.68 (1H, m), 7.42 (1H, d), 7.50 (1H, t), 7.54 (1H, s), 7.81 (1, d), 8.27 (1H, d), 8.65 (1H, s), 10.66 (1H, s),

Elemental analysis values as C23H18N6 OS/1 /4 H2 O

Theoretical values (%) C, 64.10, H, 4.33,N, 19.5,

Measured values (%) C, 63.83, H, 4.17, N, 19.59..

(0442)

Example 143

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-(4-(2-(4-methoxybenzyl) tetrazol-5-yl) benzoyl) glycine:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-(4-(2-(4-methoxybenzyl) tetrazol-5-yl) benzoyl) glycine ethyl ester.

3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzoic acid and N-(4-(2-(4-methoxybenzyl) tetrazol-5-yl) benzoyl) glycine ethyl ester were processed in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-(4-(2-(4-methoxybenzyl) tetrazol-5-yl) benzoyl) glycine ethyl ester was obtained as an oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.31 (3H, t), 1.88-2.41 (6H, m), 3.68 (1H, m), 3.78 (3H, s), 4.26 (2H, q), 4.60 (2H, s), 5.70 (2H, s), 6.86-6.90 (2H, m), 6.96 (1H, s), 7.11 (1H, d), 7.18 (1H, t), 7.34-7.38 (3H, m), 7.44-7.46 (3H, m), 7.97 (1H, d).

(0443)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-(4-(2-(4-methoxybenzyl) tetrazol-5-yl) benzoyl) glycine.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-(4-(2-(4-methoxybenzyl) tetrazol-5-yl) benzoyl) glycine ethyl ester was processed in the same way as in Example 56, and the title substance was obtained.

mp. 94-96°C,

NMR (400 MHz, DMSO-d6) δ ppm 1.83-2.32 (6H, m), 3.65 (1H, m), 3.73 (3H, s), 4.57 (2H, s), 5.88 (2H, s), 6.94 (2H, d), 7.22 (1H, d), 7.31 (1H, t), 7.36 (2H, d), 7.43-7.47 (3H, m), 7.53 (1H, s), 7.57 (1H, s), 7.92 (2H, d), 12.96 (1H, s).

(0444)

Example 144

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-(4-(1H-tetrazol-5-yl) benzoyl) glycine ethyl ester :

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-(4-(2-(4-methoxybenzyl) tetrazol-5-yl) benzoyl) glycine ethyl ester was processed in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 89-91°C,

IR v max cm-1 2216, 1746, 1660,

NMR (400 MHz, DMSO-d6) δ ppm 1.30 (3H, s), 1.83-2.32 (6H, m), 3.66 (1H, m), 4.17 (2H, q), 4.67 (2H, s), 7.26 (1H, d), 7.34 (1H, t), 7.47 (1H, d), 7.52-7.53 (3H, m), 7.61 (1H, s), 7.93 (2H, d),

MS(FAB)m/z 513 (M+ +1).

(0445)

Example 145

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-(4-(1H-tetrazol-5-yl) benzoyl) glycine :

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-(4-(1H-tetrazol-5-yl) benzoyl) glycine ethyl ester was processed in the same way as in Example 56, and the title substance was obtained.

mp. 135-138°C,

IR v max cm-1 2216, 1738, 1656,

NMR (400 MHz, DMSO-d6) δ ppm 1.86-2.33 (6H, m), 3.65 (1H, m), 4.58 (2H, s), 7.26 (1H, d), 7.33 (1H, t), 7.46 (1H, d), 7.52 (1H, s), 7.52 (2H, d), 7.59 (1H, s), 7.93 (2H, d), 12.95 (1H, s),

MS(FAB)m/z 485 (M+ +1).

(0446)

Example 146

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-methyl-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-methyl-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-N-methyl-aniline and 4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzoic acid were treated in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-methyl-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was obtained as an oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.88-2.41 (6H, m), 3.51 (3H, s), 3.68 (1H, m), 3.78 (3H, s), 5.69 (2H, s), 6.88 (2H, d), 6.96 (1H, s), 6.99 (1H, d), 7.18 (1H, t), 7.34-7.38 (4H, m), 7.41 (2H, d), 7.97 (2H, d).

(0447)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-methyl-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-methyl-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 126-128°C (decomp) (recrystallization solvent: chloroform-n-hexane),

IR v max cm-1 2216, 1650,

NMR (400 MHz, DMSO-d6) δ ppm 1.83-2.32 (6H, m), 3.42 (3H, s), 3.66 (1H, m), 7.28 (1H, d), 7.34 (1H, t), 7.45 (1H, d), 7.53 (1H, s), 7.53 (2H, d), 7.66 (1H, s), 7.91 (2H, d),

MS(FAB)m/z 441 (M+ +1),

Elemental analysis values as C24H20N6 OS/1 /4 H2 O

Theoretical values (%) C, 64.77, H, 4.64,N, 18.88,

Measured values (%) C, 64.98, H, 4.75, N, 19.04..

(0448)

Example 147

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-methyl-tetrazol-5-yl) benzamide:

Step 1

Synthesis of 4-(2-methyl-2H-tetrazol-5-yl) benzoic acid.

Methyl 4-(2-methyl-2H-tetrazol-5-yl) benzoic acid was treated in the same way as in Example 56, and 4-(2-methyl-2H-tetrazol-5-yl) benzoic acid was obtained.

NMR (400 MHz, DMSO-d6) δ ppm 4.45 (3H, s), 8.11 (2H, d), 8.18 (2H, d), 13.2 (1H, br s).

(0449)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-methyl-tetrazol-5-yl) benzamide.

4-(2-methyl-2H-tetrazol-5-yl) benzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-N-methyl-aniline were treated in the same way as in Step 2 of Example 104, and the title substance was obtained.

mp. 200-202°C (recrystallization solvent: chloroform-n-hexane),

IR v max cm-1 2216, 1656, 1606,

NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.41 (6H, m), 3.71 (1H, m), 4.46 (3H, s), 7.41 (1H, d), 7.48 (1H, t), 7.53 (1H, s), 7.88 (1H, d), 8.15-8.16 (3H, m), 8.21-8.24 (2H, m), 10.56 (1H, s),

MS(FAB)m/z 441 (M+ +1),

Elemental analysis values as C24H20N6 OS/1 /2 H2 O

Theoretical values (%) C, 64.13, H, 4.71,N, 18.70,

Measured values (%) C, 63.89, H, 4.56, N, 18.66..

(0450)

Example 148

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylphenyl)-4-(1H-tetrazol-5-yl) benzamide :

4-(2-(methoxybenzyl)-2H-tetrazol-5-yl) benzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylaniline were processed in the same way as in Step 2 of Example 104, and continuing, it was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 223-225°C (chloroform-ethanol n-hexane = recrystallization solvent),

IR v max cm-1 2208, 1640,

NMR (400 MHz, DMSO-d6) δ ppm 1.89-2.29 (6H, m), 2.43 (3H, s), 3.66-3.70 (1H, m), 7.31 (1H, t), 7.51 (1H, d), 7.53 (1H, s), 7.57 (1H, d), 8.21 (4H, s), 10.26 (1H, s),

MS(FAB)m/z 441 (M+ +1),

Elemental analysis values as C24H20N6 OS/1 /4 H2 O

Theoretical values (%) C, 64.77, H, 4.64, N, 18.88,

Measured values (%) C, 64.60, H, 4.58, N, 19.08..

(0451)

Example 149

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-methoxy-4-(1H-tetrazol-5-yl) benzamide:.

Step 1.

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-methoxy-4-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl) benzamide and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-methoxy-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

Mixture of 3-methoxy-4-(1-(methoxybenzyl)-1H-tetrazol-5-yl)benzoic acid and 3-methoxy-4-(2-(methoxybenzyl)-2H-tetrazol-5-yl) benzoic acid (1-(methoxybenzyl) : 2-(methoxybenzyl) = about 1:1) and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 1 of Example 103, and a mixture of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-methoxy-4-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl) benzamide and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-methoxy-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide (about 1:1) was obtained as straw-coloured foamed substance.

NMR (400 MHz, CDCl3) δ ppm 1.88-2.39 (6H, m), 3.70 (1H, m), 3.75, 3.77, 3.80 and 3.96 (6H, each s), 5.39 and 5.79 (2H, each s), 6.74 and 6.90 (2H, each d), 6.95-6.97 (2H, m), 7.31 (1/2 H, d), 7.38-7.42 (4H, m), 7.57-7.59 (1H, m), 7.77 (1H, m), 7.92 (1/2 H, d), 7.95 (1/2 H, d), 7.99 (1/2 H, d), 8.27 (1/2 H, s), 8.44 (1/2 H, s).

(0452)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-methoxy-4-(1H-tetrazol-5-yl) benzamide.

Compound obtained in the aforesaid Step 1 was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 197-199°C,

IR v max cm-1 2208, 1654,

NMR (400 MHz, DMSO-d6) δ ppm 1.85-2.35 (6H, m), 3.68 (1H, m), 4.10 (3H, s), 7.43 (1H, d), 7.51 (1H, t), 7.54 (1H, s), 7.77 (1H, d), 7.78 (1H, s), 8.13 (1H, s), 8.29 (1H, m), 10.58 (1H, s),

MS(FAB)m/z 457 (M+ +1),

Elemental analysis values as C24H20N6 O2 S/H2 O

Theoretical values (%) C, 60.75, H, 4.67,N, 17.71,

Measured values (%) C, 60.74, H, 4.32, N, 17.16..

(0453)

Example 150

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-methyl-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-methyl-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

3-methyl-4-(2-(methoxybenzyl)-2H-tetrazol-5-yl) benzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 1 of Example 103, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-methyl-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was obtained as a pale yellow foamed substance.

NMR (400 MHz, CDCl3) δ ppm 1.91-2.39 (6H, m), 2.71 (3H, s), 3.69 (1H, m), 3.81 (3H, s), 5.78 (2H, s), 6.92 (2H, d), 6.96 (1H, s), 7.38-7.43 (4H, m), 7.73-7.77 (2H, m), 7.82 (1H, s), 7.91 (2H, m), 8.16 (1H, d).

(0454)

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-methyl-4-(1H-tetrazol-5-yl) benzamide

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-methyl-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 128-130°C (recrystallization solvent = chloroform-methanol),

IR v max cm-1 2212, 1676, 1654,

NMR (400 MHz, DMSO-d6) δ ppm 1.87-2.35 (6H, m), 2.61 (3H, s), 3.68 (1H, m), 7.41 (1H, d), 7.49 (1H, t), 7.54 (1H, s), 7.87-7.98 (3H, m), 8.02 (1H, s), 8.14 (1H, s), 8.29 (1H, m), 10.54 (1H, s),

MS(FAB)m/z 441 (M+ +1),

Elemental analysis values as C24H20N6 OS/1 /2 H2 O

Theoretical values (%) C, 64.13, H, 4.71,N, 18.70,

Measured values (%) C, 64.44, H, 4.71, N, 18.70..

(0455)

Example 151

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-6-(1H-tetrazol-5-yl)-2-thiophene carboxamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-6-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-thiophene carboxamide.

5-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-thiophencarboxylic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 1 of Example 103, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-6-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-thiophene carboxamide was obtained as a pale yellow foamed substance.

NMR (400 MHz, CDCl3) δ ppm 1.91-2.39 (6H, m), 3.70 (1H, m), 3.81 (3H, s), 5.73 (2H, s), 6.91 (2H, dt), 6.96 (1H, s), 7.37-7.41 (4H, m), 7.64 (1H, d), 7.68 (1H, m), 7.78 (1H, d), 7.84 (1H, s).

(0456)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-6-(1H-tetrazol-5-yl)-2-thiophene carboxamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-6-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-thiophene carboxamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 224-228°C (recrystallization solvent = chloroform-methanol),

NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.34 (6H, m), 3.68 (1H, m), 7.41 (1H, dt), 7.49 (1H, t), 7.52 (1H, s), 7.82.

Elemental analysis values as C21H16N6 OS2

Theoretical values (%) C, 58.32, H, 3.73,N, 19.43,

Measured values (%) C, 58.26, H, 3.90, N, 19.48..

(0457)

Example 152

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-methyl-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-methyl-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

2-methyl-4-(2-(methoxybenzyl)-2H-tetrazol-5-yl) benzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 1 of Example 103, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-methyl-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was obtained.

mp. 128-130°C,

NMR (400 MHz, CDCl3) δ ppm 1.91-2.40 (6H, m), 2.56 (3H, s), 3.68 (1H, m), 3.80 (3H, s), 5.74 (2H, s), 6.91 (2H, d), 6.95 (1H, s), 7.37-7.41 (3H, m), 7.56 (1H, d), 7.70 (2H, br s), 7.89 (1H, br s), 7.98 (1H, d), 8.03 (1H, s).

(0458)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-methyl-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-methyl-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 135-137°C,

NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.33 (6H, m), 2.50 (3H, s), 3.67 (1H, m), 7.41 (1H, d), 7.48 (1H, t), 7.54 (1H, s), 7.73 (1H, d), 7.79 (1H, d), 7.98 (1H, d), 8.02 (1H, s), 8.11 (1H, s), 10.65 (1H, s),

MS(FAB)m/z 431 (M+ +1),

Elemental analysis values as C24H20N6 OS/1 /4 H2 O

Theoretical values (%) C, 64.77, H, 4.64, N, 18.88,

Measured values (%) C, 64.87, H, 4.87, N, 18.48..

(0459)

Example 153

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-methoxy-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-methoxy-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

3-methoxy-4-(2-(methoxybenzyl)-2H-tetrazol-5-yl) benzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 1 of Example 103, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-methoxy-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was obtained as a pale yellow oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.90-2.40 (6H, m), 3.70 (1H, m), 3.81 (3H, s), 4.19 (3H, s), 5.76 (2H, s), 6.92 (2H, d), 6.96 (1H, s), 7.31 (1H, d), 7.35-7.42 (4H, m), 7.83-7.90 (4H, m), 8.03 (1H, m), 9.88 (1H, s).

(0460)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-methoxy-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-methoxy-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was treated in the same way as in Step 5 of Example 1, and the title

substance was obtained.

mp. 153-155°C (chloroform-methanol-n-hexane = recrystallization solvent),

IR v max cm-1 2212, 1672,

NMR (400 MHz, DMSO-d6) δ ppm 1.83-2.33 (6H, m), 3.67 (1H, m), 4.01 (3H, s), 7.40 (1H, dd), 7.47 (1H, t), 7.54 (1H, s), 7.75 (1H, dd), 7.82-7.84 (3H, m), 8.08 (1H, s), 10.44 (1H, s),

MS(FAB)m/z 457 (M+ +1),

Elemental analysis values as C24H20N6 O2 S

Theoretical values (%) C, 63.14, H, 4.42,N, 18.41,

Measured values (%) C, 63.54, H, 4.58, N, 18.57..

(0461)

Example 154

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methoxyphenyl)-4-(1H-tetrazol-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methoxyphenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

4-(2-(methoxybenzyl)-2H-tetrazol-5-yl) benzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methoxyaniline were processed in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methoxyphenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was obtained as a pale yellow oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.94-2.40 (6H, m), 3.67-3.74 (1H, m), 3.80 (3H, s), 4.17 (3H, s), 5.76 (2H, s), 6.90-6.93 (2H, m), 6.99 (1H, s), 7.15 (1H, t), 7.32 (1H, dd), 7.40-7.42 (2H, m), 7.98-8.00 (2H, m), 8.27-8.29 (2H, m), 8.59 (1H, dd), 8.65 (1H, s).

(0462)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methoxyphenyl)-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methoxyphenyl)-2-methoxy-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 186-187°C (decomp) (recrystallization solvent: chloroform-n-hexane) IR v max cm-1 2216, 1658,

NMR (400 MHz, DMSO-d6) δ ppm 1.86-2.31 (6H, m), 3.63-3.72 (1H, m), 3.97 (3H, s), 7.24 (1H, t), 7.51 (1H, dd), 7.55 (1H, s), 7.86 (1H, dd), 8.19 (2H, d), 8.22 (2H, d), 10.04 (1H, s),

MS(FAB)m/z 457 (M+ +1),

Elemental analysis values as C24H20N6 O2 S/1 /2 H2 O
Theoretical values (%) C, 61.92,H, 4.55,N, 18.05,
Measured values (%) C, 62.18, H, 4.53, N, 18.27..

(0463)

Example 155

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(1H-tetrazol-5-yl)-2-trifluoromethoxy benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-trifluoromethoxy benzamide.

4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-trifluoromethoxybenzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-trifluoromethoxy benzamide was obtained.
mp. 97-100°C (decomp) (recrystallization solvent = chloroform-n-hexane) IR v max cm-1 3288, 2940, 2216, 1656, 1608, 1586, 1548, 1514,
NMR (400 MHz, CDCl3) δ ppm 1.89-2.42 (6H, m), 3.66-3.74 (1H, m), 3.81 (3H, s), 5.77 (2H, s), 6.91-6.93 (2H, m), 6.96 (1H, s), 7.37-7.43 (4H, m), 7.69-7.72 (1H, m), 7.89 (1H, s), 8.14 (1H, s), 8.22 (2H, s), 8.39 (1H, s),
MS(EI)m/z 630(M+),
Elemental analysis values as C32H25F3N6 O3 S
Theoretical values (%) C, 60.95, H, 4.00, N, 13.33,
Measured values (%) C, 60.69, H, 4.16, N, 13.54..

(0464)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(1H-tetrazol-5-yl)-2-trifluoromethoxy benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-methoxy-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-trifluoromethoxy benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 199-202°C (decomp) (recrystallization solvent = chloroform) IR v max cm-1 3316, 3104, 2976, 2948, 2868, 2212, 1658, 1624, 1608, 1584, 1548,
NMR (400 MHz, DMSO-d6) δ ppm 1.83-2.31 (6H, m), 3.63-3.72 (1H, m), 7.44 (1H, d), 7.50 (1H, t), 7.54 (1H, s), 7.75 (1H, d), 8.01 (1H, d), 8.06 (1H, s), 8.14 (1H, s), 8.22 (1H, d), 10.87 (1H, s),

MS(FAB)m/z 511 (M+ +1),
Elemental analysis values as C24H17F3 N6 O2 S/0.25H2 O
Theoretical values (%) C, 55.97, H, 3.42, N, 16.32,
Measured values (%) C, 55.88, H, 3.42, N, 16.44..

(0465)

Example 156

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(1H-tetrazol-5-yl)-2-trifluoromethyl benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-trifluoromethyl benzamide.

4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-trifluoromethyl benzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 1 of Example 103, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-trifluoromethyl benzamide was obtained as a pale yellow oily substance.
NMR (400 MHz, CDCl3) δ ppm 1.88-2.41 (6H, m), 3.63-3.72 (1H, m), 3.81 (3H, s), 5.76 (2H, s), 6.91-6.94 (2H, m), 6.95 (1H, s), 7.36-7.42 (4H, m), 7.66-7.69 (1H, m), 7.73 (1H, s), 7.74 (1H, d), 7.84 (1H, s), 8.36 (1H, d), 8.49 (1H, s).

(0466)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(1H-tetrazol-5-yl)-2-trifluoromethyl benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-trifluoromethyl benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 201-205°C (decomp) (recrystallization solvent = ethanol-n-hexane),
IR v max cm-1 3280, 2948, 2216, 1662, 1608, 1580, 1538,
NMR (400 MHz, DMSO-d6) δ ppm 1.86-2.31 (6H, m), 3.63-3.71 (1H, m), 7.44 (1H, d), 7.50 (1H, t), 7.54 (1H, s), 7.72 (1H, d), 8.03 (1H, d), 8.05 (1H, s), 8.46 (1H, d), 8.48 (1H, s), 10.93 (1H, s),
MS(EI)m/z 494(M+),
Elemental analysis values as C24H17F3 N6 OS
Theoretical values (%) C, 58.29, H, 3.46,N, 17.00,
Measured values (%) C, 58.11, H, 3.61, N, 16.73..

(0467)

Example 157

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-fluorobenzamide.

2-fluoro-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was obtained as a pale yellow oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.91-2.08 (2H, m), 2.29-2.41 (4H, m), 3.65-3.77 (1H, m), 3.80 (3H, s), 5.75 (2H, s), 6.90-6.92 (2H, m), 6.95 (1H, s), 7.36-7.41 (4H, m), 7.72-7.74 (1H, m), 7.92 (1H, s), 7.97 (1H, d), 8.08 (1H, dd), 8.28 (1H, t), 8.50 (1H, d).

(0468)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 179-181°C (decomp) (recrystallization solvent = chloroform-ethanol),

IR v max cm-1 3268, 2980, 2936, 2216, 1650, 1606, 1582, 1556,

NMR (400 MHz, DMSO-d6) δ ppm 1.86-2.03 (2H, m), 2.19-2.33 (4H, m), 3.63-3.71 (1H, m), 7.43 (1H, d), 7.49 (1H, t), 7.53 (1H, s), 7.78 (1H, d), 7.94 (1H, t), 7.98-8.03 (2H, m), 8.08 (1H, s), 10.78 (1H, s),

MS(FAB)m/z 445 (M+ +1),

Elemental analysis values as C23H17FN6 OS/0.75H2 O

Theoretical values (%) C, 60.32, H, 4.07, N, 18.35,

Measured values (%) C, 60.41, H, 3.84, N, 18.10..

(0469)

Example 158

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-fluoro-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-fluoro-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

3-fluoro-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-fluoro-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was obtained as a pale yellow oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.90-2.07 (2H, m), 2.27-2.37 (4H, m), 3.63-3.72 (1H, m), 3.79 (3H, s), 5.78 (2H, s), 6.89-6.91 (2H, m), 6.95 (1H, s), 7.37-7.41 (4H, m), 7.71-7.76 (3H, m), 7.86 (1H, s), 8.18-8.22 (2H, m).

(0470)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-fluoro-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-fluoro-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 224-226°C (decomp) (recrystallization solvent = chloroform-ethanol),

IR v max cm-1 2976, 2940, 2864, 2212, 1686, 1628, 1604, 1582, 1548,

NMR (400 MHz, DMSO-d6) δ ppm 1.86-2.03 (2H, m), 2.21-2.33 (4H, m), 3.63-3.71 (1H, m), 7.43 (1H, d), 7.50 (1H, t), 7.54 (1H, s), 7.87 (1H, d), 8.03 (1H, d), 8.07 (1H, d), 8.14 (1H, s), 8.25 (1H, t), 10.63 (1H, s),

MS(FAB)m/z 445 (M+ +1),

Elemental analysis values as C23H17FN6 OSF/0.25H2 O

Theoretical values (%) C, 61.53, H, 3.93, N, 18.72,

Measured values (%) C, 61.25, H, 3.94,N, 18.39..

(0471)

Example 159

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(4-fluoro phenoxy) methyl-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of 2-(4-fluoro phenoxy) methyl-4-(2-(2-(trimethylsilyl) ethoxymethyl)-2H-tetrazol-5-yl) benzoic acid.

Methyl 2-(4-fluoro phenoxy) methyl-4-(2-(2-(trimethylsilyl) ethoxymethyl)-2H-tetrazol-5-yl) benzoic acid was treated in the same way as in Example 56, and 2-(4-fluoro phenoxy) methyl-4-

(2-(2-(trimethylsilyl) ethoxymethyl)-2H-tetrazol-5-yl) benzoic acid was obtained.
mp. 102-104°C,
NMR (400 MHz, CDCl3) δ ppm-0.01 (9H, s), 0.97 (2H, t), 3.76 (2H, t), 5.54 (2H, s), 5.96 (2H, s), 7.02 (4H, m), 8.25 (1H, d), 8.29 (1H, d), 8.65 (1H, s).

(0472)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(4-fluoro phenoxy) methyl-4-(1 or 2H-tetrazol-5-yl) benzamide.

Oily substance which 3-fluoro-4-(2-(2-(trimethylsilyl) ethoxymethyl-2H-tetrazol-5-yl) benzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 2 of Example 104, and was obtained was deprotected in the same way as in Step 2 of Example 76 sequentially, and the title substance was obtained.
mp. 98-99°C (recrystallization solvent = chloroform-methanol),
IR ÉÀ maxcm-12216, 1674,
NMR (400 MHz, DMSO-d6) δ ppm 1.86-2.32 (6H, m), 3.67 (1H, quint), 5.38 (2H, s), 6.99-7.02 (2H, m), 7.08-7.12 (2H, m), 7.40 (1H, d), 7.46 (1H, t), 7.53 (1H, s), 7.75 (1H, d), 7.89 (1H, d), 8.06 (1H, s), 8.15 (1H, d), 8.33 (1H, s), 10.76 (1H, s),
MS(FAB)m/z 551 (M+ +1),
Elemental analysis values as C30H23FN6 O2 S/0.25H2 O
Theoretical values (%) C, 64.91, H, 4.27, N, 15.14,
.Measured values (%) C, 64.87, H, 4.30, N, 15.19..

(0473)

Example 160

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3,5-dimethoxy-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3,5-dimethoxy-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

3, 5-dimethoxy-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 1 of Example 103, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3,5-dimethoxy-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was obtained as a pale yellow oily substance.
NMR (400 MHz, CDCl3) δ ppm 1.88-2.40 (6H, m), 3.46 (6H, s), 3.65-3.73 (1H, m), 3.73 (3H, s), 5.22 (2H, s), 6.71-6.73 (2H, m), 6.90-6.92 (2H, m), 6.96 (1H, s), 7.03 (2H, s), 7.33-7.37 (2H, m),

7.66-7.69 (1H, m), 8.17 (1H, s), 10.11 (1H, s).

(0474)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3,5-dimethoxy-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3,5-dimethoxy 3-fluoro-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 223-226°C (decomp) (recrystallization solvent = chloroform-ethanol),

IR v max cm-1 2940, 2212, 1650, 1606, 1578, 1530,

NMR (400 MHz, DMSO-d6) δ ppm 1.85-2.33 (6H, m), 3.63-3.71 (1H, m), 3.85 (6H, s), 7.37 (2H, s), 7.43 (1H, d), 7.51 (1H, t), 7.53 (1H, s), 7.89 (1H, d), 8.09 (1H, s), 10.50 (1H, s),

MS(FAB)m/z 487 (M+ +1),

Elemental analysis values as C25H22N6 O3 S/0.25H2 O

Theoretical values (%) C, 61.15, H, 4.62, N, 17.11,

Measured values (%) C, 61.05, H, 4.65, N, 16.77..

(0475)

Example 161

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2,6-dimethoxy-4-(1H-tetrazol-5-yl) benzamide:

(Step 1).

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2,6-dimethoxy-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

2, 6-dimethoxy-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2,6-dimethoxy-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was obtained.

mp. 174-178°C (decomp) (recrystallization solvent = chloroform-n-hexane),

IR v max cm-1 3348, 2940, 2212, 1684, 1612, 1584, 1534, 1514,

NMR (400 MHz, CDCl3) δ ppm 1.89-2.39 (6H, m), 3.65-3.73 (1H, m), 3.74 (3H, s), 3.94 (6H, s), 5.76 (2H, s), 6.91-6.93 (2H, m), 6.95 (1H, s), 7.35-7.41 (4H, m), 7.40 (2H, s), 7.52 (1H, s), 7.76-7.79 (1H, m), 7.84 (1H, s),

MS(EI)m/z 606(M+),

Elemental analysis values as C33H30N6O4 S/0.5H2 O
Theoretical values (%) C, 64.37, H, 5.07, N, 13.65,
Measured values (%) C, 64.63, H, 4.91, N, 13.29..

(0476)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2,6-dimethoxy-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2,6-dimethoxy-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 169-173°C (decomp) (recrystallization solvent = ethanol-n-hexane),
IR v max cm-1 2976, 2940, 2212, 1606, 1584, 1554,
NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.31 (6H, m), 3.65-3.74 (1H, m), 3.90 (6H, s), 7.37 (1H, d), 7.43 (2H, s), 7.44 (1H, t), 7.53 (1H, s), 7.73 (1H, d), 8.06 (1H, s), 10.57 (1H, s),
MS(FAB)m/z 487 (M+ +1),
Elemental analysis values as C25H22N6 O3 S
Theoretical values (%) C, 61.71, H, 4.56, N, 17.27,
Measured values (%) C, 61.43, H, 4.55, N, 17.02..

(0477)

Example 162

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-chloro-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-chloro-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

2-chloro-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-chloro-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was obtained as yellow amorphous material.
NMR (400 MHz, CDCl3) δ ppm 1.89-2.41 (6H, m), 3.65-3.73 (1H, m), 3.81 (3H, s), 5.76 (2H, s), 6.91-6.93 (2H, m), 6.96 (1H, s), 7.39-7.42 (4H, m), 7.72-7.74 (1H, m), 7.88 (1H, s), 7.89 (1H, d), 8.04 (1H, s), 8.13 (1H, d), 8.24 (1H, s).

(0478)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-chloro-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-chloro-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 213-216°C (decomp) (recrystallization solvent = ethanol-n-hexane),

IR v max cm-1 2944, 2212, 1644, 1612, 1580, 1548, 1502,

NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.33 (6H, m), 3.63-3.72 (1H, m), 7.43 (1H, d), 7.50 (1H, t), 7.54 (1H, s), 7.76 (1H, d), 7.89 (1H, d), 8.07 (1H, s), 8.13 (1H, dd), 8.22 (1H, d), 10.87 (1H, s),

MS(FAB)m/z 461 (M+ +1),

Elemental analysis values as C23H17ClN6 OS

Theoretical values (%) C, 59.93, H, 3.72, N, 18.23,

Measured values (%) C, 59.78, H, 3.79, N, 17.88..

(0479)

Example 163

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-fluorophenyl)-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-fluorophenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-fluoroaniline were processed in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-fluorophenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was obtained as a pale yellow oily substance.

IR v max cm-1 2216,

NMR (400 MHz, CDCl3) δ ppm 1.87-2.45 (6H, m), 3.71 (1H, m), 3.81 (3H, s), 5.77 (2H, s), 6.92 (2H, d), 7.00 (1H, s), 7.22 (1H, t), 7.34 (1H, m), 7.42 (2H, d), 7.99 (2H, d), 8.13 (1H, br d), 8.25-8.33 (2H, m), 8.55 (1H, m),

MS(EI)m/z 564(M+),

Elemental analysis values as C31H25FN6 O2S/0.25H2 O

Theoretical values (%) C, 65.41, H, 4.52, N, 14.77,

Measured values (%) C, 64.96, H, 4.42, N, 15.01..

(0480)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-fluorophenyl)-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-fluorophenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 249-252°C,

IR v max cm-1 3300, 2220, 1650,

NMR (400 MHz, DMSO-d6) δ ppm 1.77-2.35 (6H, m), 3.68 (1H, m), 7.35 (1H, t), 7.58 (1H, s), 7.63 (1H, m), 7.76 (1H, m), 8.22 (4H, m), 10.50 (1H, s),

MS(FAB)m/z 445 (M+ +1),

Elemental analysis values as C23H17FN6 OS/H2 O

Theoretical values (%) C, 59.73, H, 4.14, N, 18.17,

Measured values (%) C, 59.75, H, 3.93, N, 18.08..

(0481)

Example 164

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-5-chloro-2-methyl-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-5-chloro-2-methyl-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

5-chloro-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-methylbenzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-fluoroaniline were processed in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-5-chloro-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-methylbenzamide was obtained.

mp. 67-69°C (decomp) (recrystallization solvent = methanol-water),

NMR (400 MHz, CDCl3) δ ppm 1.90-2.00 (1H, m), 2.00-2.10 (1H, m), 2.20-2.40 (4H, m), 3.60-3.70 (1H, m), 3.81 (3H, s), 4.15 (3H, s), 5.81 (2H, s), 6.91 (2H, d), 7.30-7.40 (2H, m), 7.43 (1H, d), 7.71 (1H, s), 7.80 (1H, s), 7.85 (1H, d), 8.43 (1H, s).

(0482)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-5-chloro-2-methyl-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-5-chloro-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-methylbenzamide was processed in the same way as in Step 5 of Example 1, and

the title substance was obtained.

mp. 130-133°C (decomp) (recrystallization solvent = chloroform-methanol-n-hexane),

IR v max cm-1 1604, 1488, 1426, 1380, 1286,

NMR (400 MHz, DMSO-d6) δ ppm 1.80-1.90 (1H, m), 1.90-2.10 (1H, m), 2.20-2.40 (4H, m), 3.60-3.80 (1H, m), 3.95 (3H, s), 7.42 (1H, d), 7.48 (1H, t), 7.53 (1H, s), 7.62 (1H, s), 7.78 (1H, d), 7.88 (1H, s), 8.06 (1H, s), 10.52 (1H, br s),

MS(FAB)m/z 475 (M+ +1),

Elemental analysis values as C24H19ClN6 OS/H2 O

Theoretical values (%) C, 54.60, H, 3.94, N, 15.28,

Measured values (%) C, 54.87, H, 3.92, N, 15.18..

(0483)

Example 165

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-methylthio-4-(1H-tetrazol-5-yl) benzamide:.

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-methylthio-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide

4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-methylthio benzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-methylthiobenzamide was obtained as a yellow oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.91-2.08 (2H, m), 2.29-2.38 (4H, m), 2, 58 (3H, s), 3.65-3.73 (1H, m), 3.80 (3H, s), 5.57 (2H, s), 6.91 (2H, d), 6.95 (1H, s), 7.37-7.41 (4H, m), 7.77-7.84 (2H, m), 7.98-8.00 (2H, m), 8.14 (1H, d), 8.56 (1H, s).

(0484)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-methylthio-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-methylthiobenzamide was processed in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 154-156°C (decomp) (recrystallization solvent = chloroform-n-hexane),

IR v max cm-1 2212, 1650, 1606, 1582, 1542,

NMR (400 MHz, DMSO-d6) δ ppm 1.86-2.02 (2H, m), 2.18-2.31 (4H, m), 2.56 (3H, s), 3.62-3.71 (1H, m), 7.41 (1H, d), 7.48 (1H, t), 7.53 (1H, s), 7.77 (1H, d), 7.78 (1H, d), 7.98 (1H, d), 8.02 (1H, s), 8.07 (1H, s), 10.69 (1H, s),

MS(EI)m/z 473 (M+ +1),
Elemental analysis values as C24H20N6 OS2/1 /4 H2 O
Theoretical values (%) C, 60.42, H, 4.33, N, 17.62,
Measured values (%) C, 60.61, H, 4.39, N, 17.58..

(0485)

Example 166

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-fluorophenyl)-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-fluorophenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-fluoroaniline were processed in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-fluorophenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was obtained.
mp. 156-158°C (recrystallization solvent = chloroform-n-hexane),
IR v max cm-1 2216, 1656,
NMR (400 MHz, CDCl3) δ ppm 1.91-2.39 (6H, m), 3.65-3.74 (1H, m), 3.80 (3H, s), 5.76 (2H, s), 6.90-6.92 (2H, m), 6.95 (1H, s), 7.33-7.36 (1H, m), 7.39-7.42 (2H, m), 7.98-8.00 (2H, m), 8.09 (1H, d), 8.27-8.29 (2H, m), 8.77 (1H, dd),
MS(FAB)m/z 565 (M+ +1),
Elemental analysis values as C31H25FN6 O2 S
Theoretical values (%) C, 65.94, H, 4.46, N, 14.89,
Measured values (%) C, 65.90, H, 4.46, N, 14.77..

(0486)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-fluorophenyl)-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-fluorophenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 218-220°C (decomp) (recrystallization solvent = chloroform-ethanol-n-hexane),
IR v max cm-1 2216, 1650,
NMR (400 MHz, DMSO-d6) δ ppm 1.85-2.31 (6H, m), 3.62-3.71 (1H, m), 7.44-7.48 (1H, m), 7.53 (1H, s), 7.58-7.62 (1H, m), 7.98 (1H, dd), 8.18-8.23 (4H, m), 10.46 (1H, s),

MS(FAB)m/z 445 (M+ +1),
Elemental analysis values as C23H17FN6 OS
Theoretical values (%) C, 62.14, H, 3.86, N, 18.91,
Measured values (%) C, 61.85, H, 3.93, N, 18.78..

(0487)

Example 167

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(1H-tetrazol-5-yl)-5-pyridinecarboxamide:
Step 1.
Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1-(2-(4-methoxybenzyl)-1H-tetrazol-5-yl)-5-pyridinecarboxamide and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-5-pyridinecarboxamide.

6-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) nicotinic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline are treated in the same way as in Step 1 of Example 103 and a mixture of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1-(2-(4-methoxybenzyl)-1H-tetrazol-5-yl)-5-pyridinecarboxamide and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-5-pyridinecarboxamide (about 1: 1) was obtained.
mp. 208-230°C (recrystallization solvent = chloroform-n-hexane),
IR v max cm-1 1690,
NMR (400 MHz, DMSO-d6) δ ppm 3.70 and 3.75 (3H, each s), 5.97 and 6.13 (2H, each s), 6.88-6.98 (2H, m), 7.31-7.43 (2H, m), 8.26 and 8.38 (1H, each d), 8.45 and 8.52 (1H, each dd), 9.19 and 9.31 (1H, each d), 13.69 (1H, br s),
MS(EI)m/z 311(M+),
Elemental analysis values as C15H13N5 O3
Theoretical values (%) C, 57.88, H, 4.216, N, 22.50,
Measured values (%) C, 58.24, H, 4.25, N, 22.55..

(0488)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-(1H-tetrazol-5-yl)-5-pyridinecarboxamide.

Compound of the aforesaid Step 1 was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 149-153°C (decomp) (recrystallization solvent = chloroform-ethanol),
IR v max cm-1 2212, 1642,

NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.35 (6H, m), 3.65-3.72 (1H, m), 7.44 (1H, d), 7.52 (1H, t), 7.54 (1H, s), 7.87 (1H, d), 8.14 (1H, s), 8.41 (1H, d), 8.59 (1H, dd), 9.30 (1H, d), 10.79 (1H, s),
MS(FAB)m/z 428 (M+ +1),
Elemental analysis values as C22H17N7 OS/1 /4 H2 O
Theoretical values (%) C, 61.17, H, 4.08, N, 22.70,
Measured values (%) C, 61.04, H, 4.14, N, 22.52..

(0489)

Example 168

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2,6-dimethyl-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2,6-dimethyl-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2,6-dimethylbenzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2,6-dimethylbenzamide was obtained as a pale yellow amorphous material.
NMR (400 MHz, CDCl3) δ ppm 1.89-2.41 (6H, m), 2.44 (6H, s), 3.65-3.73 (1H, m), 3.81 (3H, s), 5.74 (2H, s), 6.90-6.93 (2H, m), 6.96 (1H, s), 7.36-7.41 (4H, m), 7.52 (1H, br s), 7.67-7.70 (1H, m), 7.83 (2H, s), 7.91 (1H, s).

(0490)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2,6-dimethyl-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2,6-dimethylbenzamide was processed in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 218-222°C (decomp) (recrystallization solvent = ethanol-n-hexane),
IR v max cm-1 2212, 1656,
NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.35 (6H, m), 2.40 (6H, s), 3.63-3.71 (1H, m), 7.42 (1H, d), 7.48 (1H, t), 7.53 (1H, s), 7.76 (1H, d), 7.83 (2H, s), 8.10 (1H, s), 10.74 (1H, s),
MS(FAB)m/z 455 (M+ +1),
Elemental analysis values as C25H22N6 OS/1 /2 H2 O
Theoretical values (%) C, 64.78, H, 5.00, N, 18.13,

Measured values (%) C, 65.02, H, 5.03, N, 17.83..

(0491)

Example 169

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-bromo-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-bromo-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-bromobenzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-bromo benzamide was obtained as amorphous material.

NMR (400 MHz, CDCl3) δ ppm 1.89-2.41 (6H, m), 3.69 (1H, m), 3.74 (3H, s), 5.65 (2H, s), 6.74-7.81 (13H, m).

(0492)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-bromo-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-bromo benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 173-175°C (recrystallization solvent = chloroform-methanol),

IR v max cm-1 2212, 1662, It is 505((M+) +1),

NMR (400 MHz, DMSO-d6) δ ppm 1.88-2.28 (6H, m), 3.66 (1H, m), 7.38 (1H, d), 7.44 (1H, t), 7.52 (1H, s), 7.63 (1H, d), 7.74 (1H, d), 7.96 (2H, s), 8.11 (1H, s), 10.68 (1H, s),

MS(FAB)m/z 507.

Elemental analysis values as C23H17BrN6 OS

Theoretical values (%) C, 54.66, H, 3.39, N, 16.63,

Measured values (%) C, 54.30, H, 3.86, N, 16.42..

(0493)

Example 170

Methyl N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) aminocarbonyl-3-(1H-tetrazol-5-yl) benzoate:

Step 1

Synthesis of methyl N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) aminocarbonyl-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzoate.

Triethylamine 5ml and DMSO 15ml was added to methyl 3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-5-bromobenzoic acid 1 g, 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline 695 mg, 1, 3-bis (diphenyl phosphino) propane 52 mg and palladium (2) acetate 28 mg. The reaction system was substituted with carbon monoxide gas and was stirred at 120°C for ten hours. After cooling, the reaction liquor was concentrated. Toluene 100 ml were added, and next, this was washed with saturated aqueous sodium chloride solution and thereafter, was dried with sodium sulfate. The residue obtained by elimination by distillation of the solvent was purified by column chromatography (eluate = n-hexane : ethyl acetate = 3 : 1) using silica gel, and it was crystallised from the ether, and methyl N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) aminocarbonyl-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzoate was obtained.

mp. 112-120°C (recrystallization solvent = chloroform-n-hexane),

IR v max cm-1 2212, 1728,

NMR (400 MHz, CDCl3) δ ppm 1.87-2.44 (6H, m), 3.70 (1H, m), 3.81 (3H, s), 4.00 (3H, s), 5.78 (2H, s), 6.93 (2H, d), 6.97 (1H, s), 7.38-7.45 (4H, m), 7.73 (1H, m), 7.95 (1H, br s), 8.01 (1H, br s), 8.61 (1H, t), 8.82 (1H, t), 8.97 (1H, t),

MS(FAB)m/z 605 (M+ +1),

Elemental analysis values as C33H28N6 O4 S

Theoretical values (%) C, 64.58, H, 4.76, N, 13.70,

Measured values (%) C, 64.55,H, 4.66, N, 13.36..

(0494)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-methylthio-4-(1H-tetrazol-5-yl) benzamide.

Methyl N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl) aminocarbonyl-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzoate was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 190°C (decomp) (recrystallization solvent = chloroform-ethanol),

IR v max cm-1 2212, 1730,

NMR (400 MHz, DMSO-d6) δ ppm 1.82-2.36 (6H, m), 3.68 (1H, m), 3.99 (3H, s), 7.45 (1H, d), 7.52 (1H, t), 7.54 (1H, s), 7.91 (1H, d), 8.15 (1H, s), 8.73 (1H, s), 8.83 (1H, s), 8.93 (1H, s), 10.85 (1H, s),

MS(FAB)m/z 485 (M+ +1),

Elemental analysis values as C25H20N6 O3 S/1 /2 H2 O

Theoretical values (%) C, 60.84, H, 4.29, N, 17.03,
Measured values (%) C, 60.59, H, 4.17, N, 16.85..

(0495)

Example 171)

N-(3-(2-(4-cyclobutyl-2-thiazolyl)ethinyl) phenyl)-2-ethyl-4-(1H-tetrazol-5-yl) benzamide

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl)ethinyl)phenyl)-2-ethyl-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-ethyl benzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-ethyl benzamide was obtained as amorphous material.

NMR (400 MHz, CDCl3) δ ppm 1.26 (3H, t), 1.91-2.39 (6H, m), 2.93 (2H, q), 3.69 (1H, m), 3.81 (3H, s), 5.76 (2H, s), 6.92 (2H, d), 6.95 (1H, s), 7.30-8.10 (10H, m).

(0496)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-ethyl-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-ethylmethyl thiobenzamide was processed in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 160-162°C (recrystallization solvent = ethyl acetate-n-hexane),
IR v max cm-1 2216, 1652,
NMR (400 MHz, DMSO-d6) δ ppm 1.26 (3H, t), 1.87-2.33 (6H, m), 2.85 (2H, q), 3.67 (1H, m), 7.41 (1H, d), 7.48 (1H, t), 7.53 (1H, s), 7.63 (1H, d), 7.99 (1H, d), 8.05 (1H, s), 10.69 (1H, s),
MS(FAB)m/z 455 (M+ +1),
Elemental analysis values as C25H22N6 OS/3 /4 H2 O
Theoretical values (%) C, 64.15, H, 5.06, N, 17.96,
Measured values (%) C, 64.43, H, 5.13, N, 17.65..

(0497)

Example 172

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-vinyl-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-vinyl-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-vinyl benzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 1 of Example 103, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-vinyl benzamide was obtained as amorphous material.

NMR (400 MHz, CDCl3) δ ppm 1.91-2.39 (6H, m), 3.68 (1H, m), 3.81 (3H, s), 5.51 (1H, d), 5.76 (2H, s), 5.91 (1H, d), 6.69-8.35 (14H, m).

(0498)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-vinyl-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-vinyl benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 168-172°C (decomp) (recrystallization solvent = ethyl acetate-n-hexane),

IR v max cm-1 2212, 1646,

NMR (400 MHz, DMSO-d6) δ ppm 1.83-2.34 (6H, m), 3.67 (1H, m), 5.51 (1H, d), 6.00 (1H, d), 7.04 (1H, dd), 7.42 (1H, d), 7.48 (1H, t), 7.53 (1H, s), 7.77-7.80 (2H, m), 8.07-8.10 (2H, m), 8.43 (1H, s), 10.76 (1H, s),

MS(FAB)m/z 453 (M+ +1),

Elemental analysis values as C25H20N6 OS

Theoretical values (%) C, 66.35, H, 4.45, N, 18.15,

Measured values (%) C, 66.19, H, 4.44, N, 17.79..

(0499)

Example 173

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2,6-difluoro-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2,6-difluoro-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-2,6-difluoro benzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 1 of Example 103, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2,6-difluorobenzamide was obtained.

mp. 150-153°C (recrystallization solvent = chloroform-n-hexane),
IR v max cm-1 2216, 1658,
NMR (400 MHz, CDCl3) δ ppm 1.89-2.41 (6H, m), 3.64-3.73 (1H, m), 5.75 (2H, s), 6.91-6.93 (2H, m), 6.95 (1H, s), 7.36-7.41 (4H, m), 7.71-7.73 (1H, m), 7.76 (2H, d), 7.87 (2H, s),
MS(EI)m/z 512(M+),
Elemental analysis values as C31H24F2 N6 O2S
Theoretical values (%) C, 63.91, H, 4.15, N, 14.42,
Measured values (%) C, 64.14, H, 4.21, N, 14.40..

(0500)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2,6-difluoro-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2,6-difluorobenzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 227-233°C (decomp) (recrystallization solvent = ethanol-n-hexane),
IR v max cm-1 2212, 1664,
NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.31 (6H, m), 3.63-3.71 (1H, m), 7.46 (1H, d), 7.51 (1H, t), 7.54 (1H, s), 7.72 (1H, d), 7.90-7.92 (2H, m), 8.05 (1H, s), 11.15 (1H, s),
MS(FAB)m/z 463 (M+ +1),
Elemental analysis values as C23H16F2 N6 OS
Theoretical values (%) C, 59.73, H, 3.49, N, 18.17,
Measured values (%) C, 59.83, H, 3.60, N, 18.19..

(0501)

Example 174

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-6-methylthio-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-6-methylthio-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-fluoro-6-methylthio benzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-fluoro-6-methylthiobenzamide was obtained as yellow amorphous material.

NMR (400 MHz, CDCl3) δ ppm 1.91-2.40 (6H, m), 2.58 (3H, s), 3.65-3.73 (1H, m), 5.76 (2H, s), 6.91-6.93 (2H, m), 6.96 (1H, s), 7.38-7.42 (4H, m), 7.67-7.70 (1H, m), 7.71-7.74 (1H, m), 7.76 (1H, s), 7.87 (1H, s), 7.90 (1H, s).

(0502)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-6-methylthio-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-fluoro-6-methylthiobenzamide was processed in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 182-187°C (decomp) (recrystallization solvent = ethanol-chloroform),

IR v max cm-1 2212, 1656,

NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.33 (6H, m), 2.62 (3H, s), 3.63-3.72 (1H, m), 7.44 (1H, d), 7.50 (1H, t), 7.54 (1H, s), 7.71 (1H, d), 7.75-7.78 (1H, m), 7.86 (1H, s), 8.05 (1H, s), 11.00 (1H, s),

MS(FAB)m/z 491 (M+ +1),

Elemental analysis values as C24H19FN6 OS2

Theoretical values (%) C, 58.76, H, 3.90, N, 17.13,

Measured values (%) C, 58.61, H, 4.12, N, 17.36..

(0503)

Example 175

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-6-methoxy-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-6-methoxy-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-fluoro-6-methoxybenzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-fluoro-6-methoxy benzamide was obtained as a pale yellow amorphous material.

NMR (400 MHz, CDCl3) δ ppm 1.89-2.41 (6H, m), 3.65-3.74 (1H, m), 3.81 (3H, s), 4.01 (3H, s), 5.76 (2H, s), 6.91-6.94 (2H, m), 6.95 (1H, s), 7.37-7.39 (2H, m), 7.39-7.42 (2H, m), 7.55-7.58 (1H, m), 7.58 (1H, s), 7.76-7.78 (1H, m), 7.84 (1H, s), 7.88 (1H, s).

(0504)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-6-methoxy-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-fluoro-6-methoxy benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 210-213°C (decomp) (recrystallization solvent = ethanol-chloroform),

IR v max cm-1 2216, 1680,

NMR (400 MHz, DMSO-d6) δ ppm 1.86-2.33 (6H, m), 3.63-3.71 (1H, m), 3.97 (3H, s), 7.42 (1H, d), 7.48 (1H, t), 7.53 (1H, s), 7.58 (1H, d), 7.65 (1H, s), 7.72 (1H, d), 8.05 (1H, s), 10.87 (1H, s),

MS(FAB)m/z 475 (M+ +1),

Elemental analysis values as C24H19FN6 O2 S

Theoretical values (%) C, 60.75, H, 4.04, N, 17.71,

Measured values (%) C, 60.81, H, 4.25, N, 17.62..

(0505)

Example 176

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-isopropoxy-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-isopropoxy-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-isopropoxy benzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-isopropoxy benzamide was obtained.

mp. 124-125°C (recrystallization solvent = chloroform-n-hexane),

IR v max cm-1 2212, 1670,

NMR (400 MHz, CDCl3) δ ppm 1.58 (6H, d), 1.91-2.40 (6H, m), 3.66-3.74 (1H, m), 3.80 (3H, s), 4.97-5.03 (1H, m), 5.75 (2H, s), 6.89-6.93 (2H, m), 6.96 (1H, s), 7.34-7.41 (4H, m), 7.76-7.79 (1H, m), 7.84 (1H, s), 7.86-7.88 (2H, m), 8.39 (1H, d), 10.26 (1H, s),

MS(EI)m/z 604(M+),

Elemental analysis values as C34H32N6O3 S

Theoretical values (%) C, 67.52, H, 5.33, N, 13.90,

Measured values (%) C, 67.47, H, 5.44, N, 14.02..

(0506)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-isopropoxy-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-isopropoxy benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 207-210°C (decomp) (recrystallization solvent = chloroform) IR v max cm-1 2216, 1672,

NMR (400 MHz, DMSO-d6) δ ppm 1.41 (6H, d), 1.86-2.33 (6H, m), 3.63-3.71 (1H, m), 4.80-4.86 (1H, m), 7.40 (1H, d), 7.48 (1H, t), 7.53 (1H, s), 7.72-7.76 (2H, m), 7.79 (1H, s), 7.85 (1H, d), 8.09 (1H, s), 10.38 (1H, s),

MS(EI)m/z 484(M+),

Elemental analysis values as C26H24N6 O2 S

Theoretical values (%) C, 63.27, H, 5.10, N, 17.03,

Measured values (%) C, 63.39, H, 4.87, N, 17.25..

(0507)

Example 177

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-hydroxy-4-(1H-tetrazol-5-yl) benzamide :

1,2-dichloroethane 20 ml were added to 4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-isopropoxy benzoic acid 97 mg and aluminum chloride 53 mg, and the mixture was heated under reflux for 20 hours. After cooling, the reaction liquor was added to 1N hydrochloric acid 30 ml and the crystals precipitated were recovered by filtration, and the title substance was obtained.

mp. 160-163°C (decomp) (chloroform-ethanol-n-hexane = recrystallization solvent),

IR v max cm-1 2212, 1644,

NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.33 (6H, m), 3.63-3.71 (1H, m), 7.43 (1H, d), 7.49 (1H, t), 7.53 (1H, s), 7.63 (1H, dd), 7.71 (1H, d), 7.81 (1H, d), 8.08 (1H, d), 8.10 (1H, s), 10.58 (1H, s), 11.83 (1H, br s),

MS(FAB)m/z 443 (M+ +1).

(0508)

Example 178

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-nitro-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-nitro-4-(2-(4-methoxybenzyl)-

2H-tetrazol-5-yl) benzamide.

4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-nitrobenzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-nitrobenzamide was obtained as a pale yellow amorphous material.

NMR (400 MHz, CDCl3) δ ppm 1.88-2.40 (6H, m), 3.68 (1H, m), 3.81 (3H, s), 5.78 (2H, s), 6.93 (2H, d), 6.96 (1H, s), 7.39-7.83 (8H, m), 8.47 (1H, d), 8.83 (1H, s).

(0509)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-nitro-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-nitrobenzamide was processed in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. >300°C (recrystallization solvent = chloroform-methanol),

IR v max cm-1 2204, 1658, 1584, 1536, 1362, 1320,

NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.33 (6H, m), 3.67 (1H, m), 7.44 (1H, d), 7.50 (1H, t), 7.54 (1H, s), 7.69 (1H, d), 7.99 (1H, d), 8.03 (1H, s), 8.52 (1H, d), 8.78 (1H, s), 11.00 (1H, s),

Elemental analysis values as C23H17N7 O3 S

Theoretical values (%) C, 58.59, H, 3.63, N, 20.79,

Measured values (%) C, 58.20, H, 3.86, N, 20.61..

(0510)

Example 179

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-amino-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-amino-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-nitro-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was treated in the same way as in Reference Example 17, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-amino benzamide was obtained as a pale yellow amorphous material.

NMR (400 MHz, CDCl3) δ ppm 1.90-2.41 (6H, m), 3.68 (1H, m), 3.80 (3H, s), 5.67 (2H, br), 5.75 (2H, s), 6.91 (2H, d), 6.96 (1H, s), 7.38-7.56 (8H, m).

(0511)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-amino-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-amino benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 164-168°C (recrystallization solvent = chloroform-methanol),

NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.33 (6H, m), 3.67 (1H, m), 7.22 (1H, d), 7.39 (1H, t), 7.51 (1H, s), 7.53 (1H, s), 7.80 (1H, d), 7.85 (1H, d), 8.11 (1H, s), 10.32 (1H, s),

MS(FAB)m/z 442 (M+ +1),

Elemental analysis values as C23H19N7 OS/3 /4 H2 O

Theoretical values (%) C, 60.71 ,H, 4.54, N, 21.55,

Measured values (%) C, 60.88, H, 4.23, N, 21.33..

(0512)

Example 180

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-iodo-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-iodo-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-iodo benzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-iodo benzamide was obtained as amorphous material.

NMR (400 MHz, CDCl3) δ ppm 1.84-2.39 (6H, m), 3.67 (1H, m), 3.81 (3H, s), 5.75 (2H, s), 6.92 (2H, d), 6.94 (1H, s), 7.39-7.41 (4H, m), 7.61 (1H, d), 7.67 (1H, m), 7.72-7.74 (1H, m), 7.89 (1H, s), 8.18 (1H, d), 8.67 (1H, s).

(0513)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-iodo-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-iodo benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 152-154°C (decomp) (recrystallization solvent = chloroform-methanol),
NMR (400 MHz, DMSO-d6) δ ppm 1.84-2.34 (6H, m), 3.67 (1H, m), 7.43 (1H, d), 7.50 (1H, t), 7.54 (1H, s), 7.76 (2H, d), 8.07 (1H, s), 8.18 (1H, d), 8.58 (1H, s), 10.77 (1H, s),
Elemental analysis values as C23H17IN6 OS/1 /4 H2 O
Theoretical values (%) C, 49.61, H, 3.17, N, 15.09,
Measured values (%) C, 49.45, H, 3.42, N, 15.02..

(0514)
Example 181
N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-methoxy-6-methyl-4-(1H-tetrazol-5-yl) benzamide

Step 1
Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-methoxy-6-methyl-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.
4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-methoxy-6-methylbenzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-methoxy-6-methylbenzamide was obtained.
mp. 75-77°C (recrystallization solvent = water-ethanol),
NMR (400 MHz, CDCl3) δ ppm 1.90-2.30 (6H, m), 2.34 (3H, s), 3.60-3.70 (1H, m), 3.76 (3H, s), 3.88 (3H, s), 5.93 (2H, s), 6.97 (2H, d), 6.98 (1H, s), 7.39-8.08 (8H, m).

(0515)
Step 2
Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-methoxy-6-methyl-4-(1H-tetrazol-5-yl) benzamide.
N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-methoxy-6-methylbenzamide was processed in the same way as in Step 5 of Example 1, and the title substance was obtained.
mp. 181-184°C (recrystallization solvent = chloroform-methanol),
NMR (400 MHz, DMSO-d6) δ ppm 1.90-2.30 (6H, m), 2.34 (3H, s), 3.60-3.70 (1H, m), 3.76 (3H, s), 3.88 (3H, s), 7.39 (1H, t), 7.45 (1H, d), 7.53-8.08 (5H, m), 10.52 (1H, br s),
MS(FAB)m/z 471 (M+ +1),
Elemental analysis values as C25H22N6 O2 S/1 /10 H2 O
Theoretical values (%) C, 61.61, H, 4.56, N, 16.97,
Measured values (%) C, 61.87, H, 4.80, N, 16.62..

(0516)

Example 182

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-chloro-6-fluoro-4-(1 or 2H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-chloro-6-fluoro-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-chloro-6-fluorobenzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 2 of Example 104, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-chloro-6-fluorobenzamide was obtained as amorphous material.

NMR (400 MHz, CDCl3) δ ppm 1.90-2.30 (6H, m), 3.60-3.70 (1H, m), 3.76 (3H, s), 5.93 (2H, s), 6.97 (2H, d), 6.98 (1H, s), 7.39-8.08 (9H, m).

(0517)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-chloro-6-fluoro-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-chloro-6-fluorobenzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 216-236°C (recrystallization solvent = chloroform-methanol),

NMR (400 MHz, DMSO-d6) δ ppm 1.90-2.30 (6H, m), 2.34 (3H, s), 3.60-3.70 (1H, m), 3.76 (3H, s), 7.39 (1H, t), 7.45 (1H, d), 7.54-8.08 (5H, m), 10.52 (1H, br s),

MS(FAB)m/z 479 (M+ +1).

(0518)

Example 183

N-(3-(2-(4-tert-butyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-tert-butyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-fluorobenzoic acid and 3-(2-(4-tert-butyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 2 of Example 104, and N-(3-(2-

(4-tert-butyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-fluorobenzamide was obtained.

mp. 212-213°C (recrystallization solvent = chloroform-n-hexane),

IR v max cm-1 2212, 1658,

NMR (400 MHz, CDCl3) δ ppm 1.38 (9H, s), 3.80 (3H, s), 5.76 (2H, s), 6.90-6.93 (2H, m), 6.97 (1H, s), 7.36-7.42 (4H, m), 7.71-7.74 (1H, m), 7.93 (1H, s), 7.97 (1H, dd), 8.08 (1H, dd), 8.28 (1H, t), 8.50 (1H, d),

MS(FAB)m/z 567 (M+ +1),

Elemental analysis values as C31H27FN6 O2 S/1 /4 H2 O

Theoretical values (%) C, 65.19, H, 4.85, N, 14.71,

Measured values (%) C, 64.96, H, 4.80, N, 14.57..

(0519)

Step 2

Synthesis of N-(3-(2-(4-tert-butyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-tert-butyl-2-thiazolyl) ethinyl) phenyl)-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-fluorobenzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 214-216°C (decomp) (recrystallization solvent = chloroform) NMR (400 MHz, DMSO-d6) δ ppm 1.32 (9H, s), 7.47-7.50 (1H, m), 7.50 (1H, s), 7.77 (1H, d), 7.94 (1H, t), 7.98-8.03 (2H, m), 8.08 (1H, s), 10.77 (1H, s),

MS(EI)m/z 446(M+),

Elemental analysis values as C23H19FN6 OS/1 /4 H2 O

Theoretical values (%) C, 61.25, H, 4.36, N, 18.63,

Measured values (%) C, 61.36, H, 4.42, N, 18.52..

(0520)

Example 184

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-bromo-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-5-bromo-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-5-bromobenzoic acid and 3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) aniline were treated in the same way as in Step 1 of Example 103, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-5-bromo

benzamide was obtained.

mp. 167-174°C (recrystallization solvent = chloroform-n-hexane),

IR v max cm-1 2212,

NMR (400 MHz, CDCl3) δ ppm 1.87-2.44 (6H, m), 3.70 (1H, m), 3.80 (3H, s), 5.75 (2H, s), 6.92 (2H, d), 6.96 (1H, s), 7.36-7.42 (4H, m), 7.73 (1H, m), 7.90 (1H, br s), 8.07 (1H, br s), 8.15 (1H, t), 8.45 (1H, t), 8.49 (1H, br s),

MS(FAB)m/z 625 (M+ +1),

Elemental analysis values as C31H25BrN6 O2 S/H2 O

Theoretical values (%) C, 57.85, H, 3.70, N, 13.06,

Measured values (%) C, 58.11, H, 4.26,N, 13.31.

(0521)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-5-bromo-3-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-5-bromo benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 217-222°C (decomp) (recrystallization solvent = chloroform-n-hexane), It is 503((M+) +1),

NMR (400 MHz, DMSO-d6) δ ppm 1.85-2.38 (6H, m), 3.68 (1H, m), 7.32 (1H, s), 7.37 (1H, d), 7.44 (1H, t), 7.88 (1H, br d), 8.15 (1H, br t), 8.36 (1H, brt), 8.44 (1H, br t), 8.72 (1H, br t), 10.63 (1H, s),

MS(FAB)m/z 505.

Elemental analysis values as C23H17BrN6 OS/3 /4 H2 O

Theoretical values (%) C, 53.23, H, 3.59, N, 16.20,

Measured values (%) C, 53.54, H, 3.65, N, 15.72..

(0522)

Example 185

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-hydroxy-6-methyl-4-(1H-tetrazole-5-benzamide (sic):

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-methoxy-6-methyl-4-(1H-tetrazole-5-benzamide was treated in the same way as in Example 177, and the title substance was obtained (sic).

mp. 214-218°C (decomp) (recrystallization solvent = chloroform-methanol),

NMR (400 MHz, DMSO-d6) δ ppm 1.90-2.30 (6H, m), 2.34 (3H, s), 3.60-3.70 (1H, m), 7.35 (1H, t), 7.49 (1H, d), 7.53 (1H, s), 7.55 (1H, s), 7.62 (1H, s), 7.82 (1H, d), 8.08 (1H, s), 10.43 (1H, s),

10.52 (1H, s),
MS(FAB)m/z 471 (M+ +1).

(0523)

Example 186

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-hydroxy-4-(1H-tetrazol-5-yl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-hydroxy-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide.

N-(3-iodo phenyl)-N-hydroxy-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide and 4-cyclobutyl-2-einyl (sic) thiazole were processed in the same way as in Step 4 of Example 1, and N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-hydroxy-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was obtained as an oily substance.

NMR (400 MHz, CDCl3) δ ppm 1.90-2.40 (6H, m), 3.60-3.70 (1H, m), 3.80 (3H, s), 5.75 (2H, s), 6.90 (2H, d), 7.35-8.30 (12H, m).

(0524)

Step 2

Synthesis of N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-hydroxy-4-(1H-tetrazol-5-yl) benzamide.

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-N-hydroxy-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 167-170°C (decomp) (ethyl acetate-methanol = recrystallization solvent),
NMR (400 MHz, DMSO-d6) δ ppm 1.90-2.40 (6H, m), 3.60-3.70 (1H, m), 7.53 (1H, s), 7.64 (1H, t), 7.87 (1H, d), 7.92 (1H, s), 8.07 (1H, d), 8.30-8.40 (5H, m),
MS(FAB)m/z 443 (M+ +1).

(0525)

Example 187

N-(4-(1H-tetrazol-5-yl) phenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide:

Step 1

Synthesis of N-(4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) phenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide.

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzoic acid and 4-(2-(4-methoxybenzyl)-2H-tetrazol-5-

yl) aniline were treated in the same way as in Step 1 of Example 103, and N-(4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) phenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide was obtained.

mp. 179-180°C (recrystallization solvent = chloroform-n-hexane),

IR v max cm-1 2216, 1662,

NMR (400 MHz, CDCl3) δ ppm 1.94-2.40 (6H, m), 3.66-3.73 (1H, m), 3.80 (3H, s), 5.73 (2H, s), 6.89-6.92 (2H, m), 6.99 (1H, s), 7.38-7.40 (2H, m), 7.52 (1H, t), 7.75 (1H, d), 7.80 (2H, d), 7.93 (1H, d), 8.03 (1H, s), 8.06 (1H, s), 8.15 (2H, d),

MS(FAB)m/z 547 (M+ +1),

Elemental analysis values as C31H26N6 O2 S

Theoretical values (%) C, 68.11, H, 4.79, N, 15.38,

Measured values (%) C, 67.79, H, 4.81, N, 15.24..

(0526)

Step 2

Synthesis of N-(4-(1H-tetrazol-5-yl) phenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide.

N-(4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) phenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 245-246°C (decomp) (recrystallization solvent = chloroform-ethanol),

IR v max cm-1 2216, 1654,

NMR (400 MHz, DMSO-d6) δ ppm 1.96-2.32 (6H, m), 3.64-3.72 (1H, m), 7.55 (1H, s), 7.67 (1H, t), 7.89 (1H, d), 8.01-8.04 (3H, m), 8.07 (2H, d), 8.29 (1H, s), 10.65 (1H, s),

MS(FAB)m/z 427 (M+ +1),

Elemental analysis values as C23H18N6 OS/1 /4 H2 O

Theoretical values (%) C, 64.10, H, 4.33, N, 19.50,

Measured values (%) C, 63.89, H, 4.25, N, 19.37..

(0527)

Example 188

N-(3-(1H-tetrazol-5-yl) phenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide:

Step 1

Synthesis of N-(3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) phenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide.

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzoic acid and 3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) aniline were treated in the same way as in Step 2 of Example 104, and N-(3-(2-(4-

methoxybenzyl)-2H-tetrazol-5-yl) phenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide was obtained.

mp. 185-186°C (recrystallization solvent = chloroform-n-hexane),

IR v max cm-1 2216, 1658,

NMR (400 MHz, CDCl3) δ ppm 1.92-2.40 (6H, m), 3.69-3.73 (1H, m), 3.79 (3H, s), 5.72 (2H, s), 6.88-6.90 (2H, m), 6.99 (1H, s), 7.37-7.39 (2H, m), 7.46-7.51 (2H, m), 7.72-7.74 (1H, m), 7.92-7.96 (3H, m), 8.07 (1H, s), 8.17 (1H, br s), 8.29 (1H, s),

MS(FAB)m/z 547 (M+ +1),

Elemental analysis values as C31H26N6 O2 S

Theoretical values (%) C, 68.11, H, 4.79, N, 15.38,

Measured values (%) C, 67.73, H, 4.86, N, 15.22..

(0528)

Step 2

Synthesis of N-(3-(1H-tetrazol-5-yl) phenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide.

N-(3-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) phenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 162-164°C (decomp) (recrystallization solvent = chloroform-ethanol),

IR v max cm-1 2216, 1662,

NMR (400 MHz, DMSO-d6) δ ppm 1.87-2.34 (6H, m), 3.64-3.72 (1H, m), 7.55 (1H, s), 7.61 (1H, t), 7.67 (1H, t), 7.77 (1H, d), 7.89 (1H, d), 7.98 (1H, d), 8.10 (1H, d), 8.32 (1H, s), 8.62 (1H, s), 10.63 (1H, s),

MS(FAB)m/z 427 (M+ +1),

Elemental analysis values as C23H18N6 OS/1 /4 H2 O

Theoretical values (%) C, 64.10, H, 4.33, N, 19.50,

Measured values (%) C, 64.38, H, 4.33, N, 19.45..

(0529)

Example 189

N-(4-(1H-tetrazol-5-yl)-2-methoxyphenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide:

Step 1

Synthesis of N-(4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-methoxyphenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide.

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzoic acid and 2-methoxy-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) aniline were treated in the same way as in Step 1 of Example 103, and N-(4-(2-(4-

methoxybenzyl)-2H-tetrazol-5-yl)-2-methoxyphenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide was obtained as amorphous material.

NMR (400 MHz, CDCl3) δ ppm 1.90-2.42 (6H, m), 3.67-3.75 (1H, m), 3.80 (3H, s), 4.06 (3H, s), 5.74 (2H, s), 6.91 (2H, d), 6.99 (1H, s), 7.40 (2H, d), 7.53 (1H, t), 7.72 (1H, d), 7.77 (1H, d), 7.81 (1H, dd), 7.96 (1H, d), 8.08 (1H, s), 8.63 (1H, s), 8.65 (1H, d).

(0530)

Step 2

Synthesis of N-(4-(1H-tetrazol-5-yl)-2-methoxyphenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide.

N-(4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-methoxyphenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 220-221°C (decomp) (recrystallization solvent = chloroform-n-hexane),

IR v max cm-1 2216, 1682, 1656,

NMR (400 MHz, DMSO-d6) δ ppm 1.89-2.29 (6H, m), 3.66-3.72 (1H, m), 3.97 (3H, s), 7.55 (1H, s), 7.64 (1H, d), 7.67 (1H, t), 7.74 (1H, s), 7.88 (1H, d), 8.04 (1H, d), 8.05-8.08 (1H, m), 8.27 (1H, s), 9.86 (1H, s),

MS(FAB)m/z 427 (M+ +1),

Elemental analysis values as C24H20N6 O2 S/1 /2 H2 O

Theoretical values (%) C, 61.92, H, 4.55, N, 18.05,

Measured values (%) C, 62.21, H, 4.42, N, 17.94..

(0531)

Example 190

N-(4-(1H-tetrazol-5-yl) phenyl)-N-methyl-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide:

Step 1

Synthesis of N-(4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) phenyl)-N-methyl-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide.

3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzoic acid and N-methyl-4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) aniline were treated in the same way as in Step 2 of Example 104, and N-(4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) phenyl)-N-methyl-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide was obtained.

NMR (400 MHz, CDCl3) δ ppm 1.87-2.41 (6H, m), 3.53 (3H, s), 3.68 (1H, m), 3.79 (3H, s), 5.70 (2H, s), 6.88 (2H, d), 6.94 (1H, s), 7.13 (1H, d), 7.15 (1H, t), 7.24 (1H, d), 7.36 (2H, d), 7.45 (1H, d), 7.62 (1H, s), 8.01 (1H, d).

(0532)

Step 2

Synthesis of N-(4-(1H-tetrazol-5-yl) phenyl)-N-methyl-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide.

N-(4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) phenyl)-N-methyl-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide was treated in the same way as in Step 5 of Example 1, and the title substance was obtained.

mp. 114-117°C (decomp),

IR v max cm-1 2216, 1650,

NMR (400 MHz, DMSO-d6) δ ppm 1.83-2.32 (6H, m), 3.44 (3H, s), 3.65 (1H, m), 7.33 (1H, t), 7.36 (1H, d), 7.46 (2H, d), 7.52 (1H, s), 7.58 (1H, d), 7.63 (1H, s), 7.93 (2H, d),

MS(FAB)m/z 441 (M+ +1),

Elemental analysis values as C24H20N6 OS/1 /2 H2 O

Theoretical values (%) C, 64.12, H, 4.71, N, 18.70,

Measured values (%) C, 64.13, H, 4.92, N, 19.17..

(0533)

Example 191

N-(4-(1H-tetrazol-5-yl) phenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methylbenzamide :

The N-(4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) phenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-methylbenzamide obtained in the same way as above was deprotected in the same way, and the title substance was obtained.

mp. 225-228°C (decomp) (recrystallization solvent = chloroform-ethanol),

NMR (400 MHz, DMSO-d6) δ ppm 1.80-2.40 (6H, m), 2.46 (3H, s), 3.60-3.80 (1H, m), 7.45 (1H, d), 7.52 (1H, s), 7.69 (1H, d), 7.82 (1H, s), 7.97 (2H, d), 8.04 (2H, d), 10.72 (1H, br s),

MS(FAB)m/z 441 (M+ +1),

Elemental analysis values as C24H20N6 OS/1 /2 H2 O

Theoretical values (%) C, 64.12, H, 4.71, N, 18.69,

Measured values (%) C, 63.92, H, 4.65, N, 18.58..

(0534)

Example 192

N-(4-(1H-tetrazol-5-yl) phenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylbenzamide :

The N-(4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) phenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-methylbenzamide obtained in the same way as aforesaid was deprotected in the same way, and the title substance was obtained.

mp. 184-186°C (decomp) (recrystallization solvent = chloroform-methanol),
IR v max cm-1 1664,
NMR (400 MHz, DMSO-d6) δ ppm 1.80-2.40 (6H, m), 2.56 (3H, s), 3.60-3.80 (1H, m), 7.44 (1H, t), 7.55 (1H, s), 7.61 (1H, d), 7.77 (1H, d), 7.97 (2H, d), 8.04 (2H, d), 10.78 (1H, br s),
MS(FAB)m/z 441 (M+ +1),
Elemental analysis values as C24H20N6 OS/1 /2 H2 O
Theoretical values (%) C, 64.12, H, 4.71, N, 18.69,
Measured values (%) C, 64.12, H, 4.62,N, 18.52..

(0535)

Example 193

N-(4-(1H-tetrazol-5-yl)-2-methylphenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide :

N-(4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-methylphenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide obtained in the same way as aforesaid was deprotected in the same way, and the title substance was obtained.
mp. 135-138°C (decomp) (chloroform-methanol-n-hexane = recrystallization solvent),
NMR (400 MHz, DMSO-d6) δ ppm 1.80-2.40 (6H, m), 2.38 (3H, s), 3.60-3.80 (1H, m), 7.55 (1H, s), 7.60-7.70 (2H, m), 7.80-7.90 (2H, m), 8.00 (1H, s), 8.09 (1H, d), 8.30 (1H, s), 10.20 (1H, s),
MS(FAB)m/z 441 (M+ +1).

(0536)

Example 194

N-(4-(1H-tetrazol-5-yl) phenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-fluorobenzamide :

N-(4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) phenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-2-fluorobenzamide obtained in the same way as aforesaid was deprotected in the same way, and the title substance was obtained.
mp. 222-226°C (decomp) (recrystallization solvent = chloroform-methanol),
IR v max cm-1 1682,
NMR (400 MHz, DMSO-d6) δ ppm 1.90-2.40 (6H, m), 3.60-3.80 (1H, m), 7.51 (1H, t), 7.54 (1H, s), 7.90 (1H, d), 7.91 (1H, d), 7.95 (2H, d), 8.05 (2H, d), 10.86 (1H, s),
MS(FAB)m/z 445 (M+ +1).

(0537)

Example 195

N-(4-(1H-tetrazol-5-yl) phenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-fluorobenzamide :

N-(4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl) phenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl)-6-fluorobenzamide obtained in the same way as aforesaid was deprotected in the same way, and the

title substance was obtained.
mp. 226-229°C (decomp) (recrystallization solvent = chloroform-methanol),
NMR (400 MHz, DMSO-d6) δ ppm 1.90-2.40 (6H, m), 3.60-3.80 (1H, m), 7.45 (1H, d), 7.48 (1H, s), 7.60 (1H, s), 7.83 (1H, dd), 7.95 (2H, d), 8.05 (2H, d), 10.88 (1H, s),
MS(FAB)m/z 445 (M+ +1),
Elemental analysis values as C23H17FN6 OS/1 /2 H2 O
Theoretical values (%) C, 60.92, H, 4.00, N, 18.53,
Measured values (%) C, 60.73, H, 4.12, N, 18.29..

(0538)

Example 196

N-(4-(1H-tetrazol-5-yl)-2-fluorophenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide :

N-(4-(2-(4-methoxybenzyl)-2H-tetrazol-5-yl)-2-fluorophenyl)-3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) benzamide obtained in the same way as aforesaid was deprotected in the same way, and the title substance was obtained.
mp. 236-239°C (decomp) (recrystallization solvent = chloroform-methanol),
NMR (400 MHz, DMSO-d6) δ ppm 1.90-2.40 (6H, m), 3.60-3.80 (1H, m), 7.55 (1H, s), 7.68 (1H, t), 7.90-8.00 (5H, m), 8.09 (1H, d), 8.31 (1H, s), 10.54 (1H, s),
MS(FAB)m/z 445 (M+ +1).

(0539)

Example 197

Preparation Example :

Production of tablet:
The compound of Example 1 1000 mg, well pulverised, was mixed thoroughly with lactose 5900 mg, crystalline cellulose (MCC)2000mg, low degree of substitution hydroxypropylcellulose (LHPC)1000mg, magnesium stearate 100 mg, and the bare tablet which containing 10 mg of the aforesaid compound per 100 mg tablet was prepared using direct tabletting method was produced. Sugar coating or film coat was put on this bare tablet, and sugar coated tablet and film coat tablet were produced.

(0540)

Example 198

Preparation Example:

Production of tablet.
The compound of Example 157 1000 mg, well pulverised, was mixed thoroughly with lactose 5900 mg, crystalline cellulose (MCC)2000mg, low degree of substitution hydroxypropylcellulose

(LHPC)1000mg, magnesium stearate 100 mg, and the bare tablet which containing 10 mg of the aforesaid compound per 100 mg tablet was prepared using direct tabletting method was produced. Sugar coating or film coat was put on this bare tablet, and sugar coated tablet and film coat tablet were produced.

(0541)

Example 199

Preparation Example:

Production of encapsulated formulation.

The capsule tablet was produced by thoroughly mixing 1000 mg of compound of Example 1, well pulverised, with maize starch (corn starch) 3000 mg, milk sugar 6900 mg, crystalline cellulose (MCC)1000mg, magnesium stearate 100 mg, to obtain capsules of 120 mg containing 10 mg of the compound in the capsule.

(0542)

Example 200

Preparation Example :

Capsule tablet production

The capsule tablet was produced by thoroughly mixing 1000 mg of compound of Example 157, well pulverised, with maize starch (corn starch) 3000 mg, milk sugar 6900 mg, crystalline cellulose (MCC)1000mg, magnesium stearate 100 mg, to obtain capsules of 120 mg containing 10 mg of the compound in the capsule.

(0543)

Example 201

Preparation Example :

Production of inhalant.

Sorbitan mono oleate 50 mg was taken into 5 ml aluminum container for aerosol, and 1 ml Freon-11 was added, and it was suspended therein. 50 mg of well pulverised well, dried compound of Example 1 was added, and ultrasound was irradiated to disperse it. Metered dose valve of 100 μl is put on, and it was filled with 4 ml Freon-124 ml through valve under pressurised state. Inhalant (MDI) of metered dose spray containing the aforesaid compound one mg per 1 dose of 100 μl was produced.

(0544)

Example 202

Preparation Example :

Production of inhalant.

Sorbitan mono oleate 50 mg was taken into 5 ml aluminum container for aerosol, and 1 ml Freon-11 was added, and it was suspended therein. 50 mg of well pulverised well, dried compound of Example 157 was added, and ultrasound was irradiated to disperse it. Metered dose valve of 100 μl is put on, and it was filled with 4 ml Freon-124 ml through valve under pressurised state. Inhalant (MDI) of metered dose spray containing the aforesaid compound one mg per 1 dose of 100 μl was produced.

(0545)

The compound of this invention and salts thereof represented by formula (1) have inhibiting activity of for example bronchial constriction and are useful as the bronchopulmonary agent which can achieve relief and prevention such as asthma and allergic reaction or the like. The examples of pharmaceutical activity of compounds of this invention are shown in the embodiments, but the action of the compounds of this invention is not limited to the ones shown in activity examples, and the range of this invention is not restricted by the following test examples.

(0546)

Test Example 1

LTD4 antagonism test using guinea pig isolated ileum.

Hartley series male guinea pig, ileum was used, and it was measured using Magnus method. In other words, ileum was extracted from guinea pig after having been bled to death. Ileum was cut to length of 1-1.5cm, and cut open along the muscle direction, and ileum sample was produced. This sample was suspended in the Magnus tube filled with 10ml of Tyrode's solution (35°C, 95 % oxygen-5 % carbon dioxide aeration) and loaded with 1g. After contracting it three or four times with histamine (10-4M), contraction reaction of LTD4 was stabilised and action of test substance with respect to contraction of LTD4 was examined. The ileal contraction was recorded in recorder (R-64VS = science electricity) through isotonic transducer (TD-112S = Nihon Kohden). Test substance was dissolved in dimethyl sulphoxide (DMSO) and added to Magnus tube 5 minutes before LTD4 (final concentration 10^{-8}M) addition. Results are found as inhibition ratio by comparing ileal contraction of same sample due to LTD4 treated with solvent and ileal contraction using LTD4 treated with test substance, and inhibition ratio was calculated as 50 % inhibition dose (IC50) using least square method from regression line.

(0547)

Test Example 2

Histamine release inhibition test.

Sprague-Dawley series male rat (250-350 g) is bled to death by decapitation, then modified-Tyrode liquid which contains 5U / ml of heparin (NaCl 124mM, KCl 4mM, CaCl 21.0mM, MgCl20.5mM, NaH2 PO4/H2O 0.64mM, NaHCO310mM, Gulucose (sic) 5.6mM, Gelatin0.05 % (w / v)) 20ml were injected to rat intraperitoneally. It was cut open, and liquid in peritoneal cavity was recovered after having massaged abdomen lightly for 60 seconds. Centrifugation (250Xg, 4°C, five minutes) was done of peritoneal cavity liquid, and cells obtained was washed twice with modified-Tyrode liquid which did not include heparin. Mast cell was sensitised by adding anti DNP-Ig E antibody of 80 μl to this peritoneal exudate cell liquid (about 107 cells / ml) and being incubated at 37°C for 30 minutes. thereafter, mast cell number contained in peritoneal exudate cell liquid was adjusted by adding modified-Tyrode liquid which did not include heparin so as to become 8 x 105 cells/ml,. 50 μl of test solution including antigen (final concentration 30ng/ml) was added to this cell suspension 250 μl, and be incubated it at 37°C for five minutes. thereafter, reaction termination liquid (NaCl120mM, KCl5mM, EDTA1mM, Tris-HCl(pH = 7.4) 25 mM, BSA200 mg/mL)200 μl were added, and the reaction was terminated. Thereafter, histamine concentration in supernatant 250 μl from centrifugation (250Xg, 4°C, five minutes) was measured using process of Shore et al. Test substance at the same time as addition of antigen is added Inhibition effect thereof denoted it with 50 % inhibition amount (IC50) calculated using least square method from primary regression line of inhibition ratio of each concentration was shown.

(0548)

IC50 value of Example compound follows in LTD4 antagonism test and histamine release inhibition test using guinea pig isolated ileum.

(0549)

Table 1

Test substance (Example number) (IC50)	Ileal contraction inhibition ratio inhibition (IC50)	Histamine release
1	3.6×10^{-8}	6.5×10^{-8}
4	1.9×10^{-8}	1.2×10^{-7}
5	2.8×10^{-8}	1.5×10^{-7}
6	3.0×10^{-8}	1.2×10^{-7}

7	1.2×10^{-8}	9.9×10^{-9}
17	1.2×10^{-8}	7.5×10^{-7}
20	1.3×10^{-7}	2.2×10^{-7}
23	2.0×10^{-7}	1.5×10^{-7}
25	1.7×10^{-7}	1.2×10^{-7}
26	2.8×10^{-7}	1.1×10^{-8}
35	1.1×10^{-7}	1.0×10^{-7}
39	1.3×10^{-8}	1.7×10^{-7}
40	6.6×10^{-8}	2.8×10^{-7}
41	7.9×10^{-8}	3.1×10^{-7}
42	2.7×10^{-8}	2.0×10^{-6}
45	4.1×10^{-8}	1.8×10^{-6}
68	7.3×10^{-9}	3.5×10^{-8}
69	7.8×10^{-9}	1.1×10^{-7}
70	1.5×10^{-8}	7.1×10^{-7}
76	1.1×10^{-8}	2.4×10^{-7}
78	2.6×10^{-9}	5.5×10^{-7}
101	2.2×10^{-8}	5.4×10^{-7}
103	1.5×10^{-8}	1.2×10^{-9}
104	4.9×10^{-8}	1.5×10^{-8}
110	3.2×10^{-8}	1.3×10^{-7}
125	2.0×10^{-9}	2.7×10^{-8}
126	1.9×10^{-9}	2.6×10^{-7}
127	1.8×10^{-9}	3.8×10^{-7}
129	7.0×10^{-9}	7.0×10^{-7}
131	8.5×10^{-8}	1.7×10^{-7}
141	9.4×10^{-10}	5.9×10^{-9}
142	1.9×10^{-9}	5.4×10^{-7}
152	2.5×10^{-10}	1.5×10^{-8}
153	5.4×10^{-10}	7.4×10^{-9}
155	1.0×10^{-8}	7.4×10^{-9}
157	5.7×10^{-10}	9.3×10^{-9}
161	2.3×10^{-10}	7.0×10^{-9}
162	7.9×10^{-10}	1.8×10^{-9}
163	1.1×10^{-9}	8.2×10^{-8}
164	2.6×10^{-9}	1.0×10^{-7}
165	1.0×10^{-9}	9.4×10^{-9}
167	4.5×10^{-9}	1.0×10^{-7}
168	8.2×10^{-10}	3.1×10^{-8}
172	1.6×10^{-9}	4.7×10^{-10}
173	6.4×10^{-10}	4.1×10^{-8}
174	6.6×10^{-10}	4.0×10^{-8}
175	2.0×10^{-10}	1.8×10^{-8}
179	2.6×10^{-9}	8.1×10^{-8}
180	2.3×10^{-10}	2.5×10^{-8}
181	1.1×10^{-10}	5.9×10^{-8}
182	2.3×10^{-9}	2.6×10^{-8}
183	1.8×10^{-9}	5.5×10^{-9}
189	1.2×10^{-8}	1.7×10^{-8}
196	4.2×10^{-8}	7.8×10^{-8}

(0550)

Test Example 3

LTD4 induction bronchostriction inhibition test

Using Hartley series male guinea pig, trachea cannula and vein cannula were inserted under urethane anesthesia (1.5 g /5 ml / kg, i.p.). Trachea cannula was connected to artificial respirator, and artificial respiration was carried out with amount of ventilation about 10 ml / kg, ventilation frequency 60 times / minute. Propranolol (1 mg / kg) was administered intravenously 5 minutes before LTD4 administration, succinylcholine (1 mg / kg, in order to terminate spontaneousness respiration) was administered intravenously 3 minutes before LTD4 administration and indomethacin (2 mg / kg) was administered intravenously 2 minutes before LTD4 administration. After having regulated amount of ventilation so as to be airway pressure 10cmH2O / l / sec, LTD4 (4 μ g / kg) was administered intravenously, and airway constriction was induced. Test substance was suspended in 0.5 % carboxymethylcellulose (CMC) and it was administered orally in optimum administration time before induction. Airway constriction ratio was represented by percentage with respect to the maximum reaction that obstructed the airway completely, and the inhibition ratio was determined from maximum contraction ratio of test substance treated group, taking maximum contraction ratio of LTD4 solvent treated group as control. The results denoted it with 50 % inhibition amount (ID50) determined using least square method from regression line of short time inhibition ratio. ID50 value was as follows in LTD4 induction bronchostriction inhibition test of Example compound. Moreover, duration of airway constriction inhibition was measured from inhibition ratio eight hours or 12 hours after oral administration (10 mg / kg) of test substance.

(0551)

Table 2

Test substance (Example number)	ID50 (mg / kg)	activity duration (10mg/kg(p.o.) at 8h	at 12h
1	1.1	75 %	
4	1.3	60 %	
5	2.6		
6	2.4	76 %	
17	4.1		
20	3.1		
39	1.3	67 %	
42	2.7		
45	1.9		
78	5.1		
125	3.8	75 %	
127	1.9		
150	3.0		
152	0.7		

155	2.0	
157	0.4	81 %.

(0552)

Test Example 4

PCA (Passive cutaneous anaphylaxis) reaction inhibition test.

After hair shaving of back of Sprague-Dawley series male rat (170-220 g), intradermal injection (50 μl / site) of anti egg albumin rat serum (rat 48 hours PCA titer= 514-time) diluted 15 times with physiological saline in two places in back was made, and it was sensitised. 48 hours after sensitization, 0.5 % Evans blue physiological saline 1 ml including egg albumin of 5/ mg was administered intravenously, and PCA reaction was induced. After 30 minutes, it was decapitated and exsanguinated and blue-stained part of back was cut out, and dye of blue-stained skin was measured with process 2) of Katayama et al. Test substance was suspended in 0.5 % carboxymethylcellulose, and it was administered orally at optimum administration time just before induction. Results were determined as inhibition ratio from dye leakage of solvent treated group, and it was denoted with 50 % inhibition concentration (ID50) determined using least square method from regression line of inhibition ratio. ID50 value of PCA test as follows.

(0553)

Table 3

Test substance (Example number)	Inhibition ratio (ID50)
1	1.5
4	2.3
5	3.6
6	2.4
7	0.5
19	0.6
39	2.3
125	3.1
153	4.1
157	3.8

(0554)

Test Example 5

Light stability test.

Test substance was dissolved in methanol so as to become Concentration of 10 mg/mL, and it

was filtered with membrane filter. This solution was discharged at 3ml a time to transparent glass sample tube of capacity 5 ml, and sample was made. One of them was shaded from light as control, and another one of them was photoirradiated (1000lx hour: fluorescent lamp). Peak area of the said compound was obtained by reverse phase liquid chromatography under exclusion of light, and proportion remaining was determined according to following formula.

Proportion remaining (%) = peak area of sample illuminated by light / peak area of sample shaded from light x 100

Analysis conditions of liquid chromatography are as follows:

Analysis column used was Shiseido UG-120 (4.6 mm phi X250mm), and solution of 0.01 % trifluoroacetic acid aqueous solution : methanol 2:1 (v/v) was used as moving bed. Detection was performed using UV detector, and detection wavelength was as shown in following Table 4.

(0555)

As a result of light stability test, proportion remaining of double bond compound ((E)-4-((3-(2-(4-cyclobutyl-2-thiazolyl) ethenyl) phenyl) amino)-2,2-diethyl-4-oxobutyl acid (Ro24-5913) (Kokai 2-69468) and of (E)-2-((3-(2-(4-cyclobutyl-2-thiazolyl) ethenyl) phenylamino)-2-oxoethyl) benzoic acid (Kokai 6-80654)) were respectively 55.5 % and 56.4 %, , and triple bond compound (compound of Example 1,141,142 and 187) were 100 %, and production of decomposition product was not observed. Results of light stability test in solution (fluorescent lamp: 100 lx. 3 hours) is shown in Table 4.

(0556)

Table 4

Test compound	proportion remaining (%)	Detection wavelength
Compound of Example 1	101.4	315 nm
Compound of Example 141	100.4	253 nm
Compound of Example 142	99.9	312 nm
Compound of Example 187	99.9	300 nm
Compound A according to Kokai 2-69468	55.5	240 nm
Compound B according to Kokai 6-80654	101.4	315 nm

A: (E)-4-((3-(2-(4-cyclobutyl-2-thiazolyl) ethenyl) phenyl) amino)-2,2-diethyl-4-oxobutyric acid (Ro24-5913)

B: (E)-2-((3-(2-(4-cyclobutyl-2-thiazolyl) ethenyl) phenylamino)-2-oxoethyl) benzoic acid.

(0557)

Test Example 6

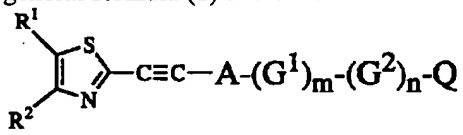
Safety Test

Compound of Example 1, 4, 6, 7, 39 was administered orally to Sprague-Dawley series rats at 250 mg/kg daily for 14 days, and there were no cases of death with any of the compounds.

Amended Claims (Amended on October 15, 2004)

Claim 1

A compound represented by general formula (1) and salts thereof



(1)

(wherein, R1 and R2 each independently denote hydrogen atom, halogen atom, optionally substituted alkyl group, optionally substituted cycloalkyl group, or a ring formed by linking R1 and R2 together. A denotes optionally substituted phenyl group, optionally substituted pyridyl group, optionally substituted furyl group, optionally substituted thienyl group, optionally substituted benzofuranyl group, optionally substituted benzo (b) thienyl group, optionally substituted benzoxazolyl group, optionally substituted benzothiazolyl group, optionally substituted pyrido (1,2-a) pyrimidinyl group, optionally substituted quinazolinyl group, optionally substituted benzo triazinyl group or optionally substituted 2H-chromenyl group. G1 denotes oxygen atom, carbonyl group, ethynyl group, group -NR3CO-, group -NR4-, group -NR5SO2-, group -SO2NR6-, group -CONR7-, group -C(=CHR8)- or group -CR9=CR10- (wherein, R3, R4, R5, R6 and R7 denote hydrogen atom, hydroxy group or optionally substituted alkyl group, R8 denotes cyano group, carboxyl group or optionally substituted alkoxycarbonyl group. R9 and R10 each independently denote hydrogen atom, halogen atom, optionally substituted alkyl group, optionally substituted cycloalkyl group, optionally substituted aryl group or a ring formed by linking R9 and R10 together), G2 denotes optionally substituted phenyl group, optionally substituted pyridyl group, optionally substituted thiazolyl group, optionally substituted isoxazolyl group, optionally substituted thienyl group, optionally substituted pyrimidinyl group, group -CHR11-CHR12- or group -CR13=CR14-(CR15=CR16) y- (wherein, in the formula R11 and R12 denote a ring formed by linking together, R13, R14, R15 and R16 each independently denote hydrogen atom, halogen atom, optionally substituted alkyl group, optionally substituted aryl group, a ring formed by linking R13 and R14 or R15 and R16 together, and y denotes an integer of 0-3), m and n each independently denote an integer of 0 or 1. Q denotes a group represented by (sic) carboxyl group, optionally substituted alkoxycarbonyl group, -CONH-(5-tetrazolyl) group, optionally substituted 5-tetrazolyl group, optionally substituted 1,2,3-triazolyl group, optionally substituted 2,4-dioxo thiazolidine-5-ylidenyl group, optionally substituted 4-oxo-2-thioxo thiazolidine-5-ylidenyl group, optionally substituted 5-oxo-4-tetrazolyl group, optionally substituted 3-(5-oxo)-(1,2,4) oxadiazolidinyl group, optionally substituted 2-(3,5-dioxo)-(1,2,4) oxadiazolinyl group, optionally substituted 5-(3-oxo)-(1,2,4) oxadiazolidinyl group or optionally substituted 3-(5-oxo)-iso oxazolidyl group).

(Wherein, the case in which m and n are 0 and Q is carboxyl group or alkoxycarbonyl group is

excluded.)

Claim 2

A compound in accordance with Claim 1 and salts thereof, wherein R1 in formula (1) is hydrogen atom.

Claim 3

A compound in accordance with any one of the Claim 1-2 and salts thereof, wherein R2 in formula (1) is optionally substituted alkyl group or optionally substituted cycloalkyl group.

Claim 4

A compound in accordance with any one of Claims 1-3 and salts thereof, wherein A in formula (1) is optionally substituted phenyl group.

Claim 5

A compound in accordance with any one of Claims 1-4 and salts thereof, wherein a group represented by A in formula (1) is phenyl group, and 2-ethinyl thiazolyl group and a group represented by (G1)m-(G2)n-Q are meta configuration.

Claim 6

A compound in accordance with any one of Claims 1-5 and salts thereof, wherein Q in formula (1) is 5-tetrazolyl group.

Claim 7

A compound in accordance with any one of Claims 1-6 and salts thereof, wherein m and n in formula (1) is 0.

Claim 8

A compound in accordance with any one of Claims 1-6 and salts thereof, wherein m and n in formula (1) is 1, G1 is -NR3CO- and G2 is phenyl group which may have one or more substituents.

Claim 9

A compound in accordance with any one of Claims 1-6 or Claim 8 and salts thereof, wherein G2 in formula (1) is phenyl group which may have one or more substituents, and G1 and Q are para configuration.

Claim 10

A compound in accordance with any one of Claims 1-6 and salts thereof, wherein m and n in formula (1) is 1, G1 is -NR3CO- and G2 is –CR13=CR14-(CR15=CR16)y-.

Claim 11

A drug formed from a compound in accordance with any one of Claims 1-10 or salts thereof.

Claim 12

A drug for prevention and/or therapy of allergic disease containing as effective ingredient a compound in accordance with any one of Claims 1-10 or salts thereof.

Claim 13

A drug for prevention and/or therapy of disease in accordance with Claim 12, wherein the allergic disease is an allergic disease involving leukotriene.

Claim 14

A drug for prevention and/or therapy of disease in accordance with Claim 12, wherein the allergic disease is an allergic disease involving histamine.

Claim 15

A drug for prevention and/or therapy of disease in accordance with Claim 12, wherein the allergic disease is an allergic disease simultaneously involving leukotriene and histamine.

Claim 16

5-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-1H-tetrazole.

Claim 17

(E)-N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-3-(1H-tetrazol-5-yl) propenamide.

Claim 18

N-(3-(2-(4-cyclobutyl-2-thiazolyl) ethinyl) phenyl)-2-fluoro-4-(1H-tetrazol-5-yl) benzamide.

Rising Sun Communications Ltd. Terms and Conditions (Abbreviated)

Rising Sun Communications Ltd. shall not in any circumstances be liable or responsible for the accuracy or completeness of any translation unless such an undertaking has been given and authorised by Rising Sun Communications Ltd. in writing beforehand. More particularly, Rising Sun Communications Ltd. shall not in any circumstances be liable for any direct, indirect, consequential or financial loss or loss of profit resulting directly or indirectly from the use of any translation or consultation services by the customer.

The Full Terms and Conditions of Business of Rising Sun Communications may be found at the web site address <http://www.risingsun.co.uk/Terms_of_business.html>